Procalcitonin: A Severity Marker for Pre-Eclampsia?

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Abstract: *Introduction*: Pre-eclampsia is a common and potentially dangerous disorder of human pregnancy. The maternal syndrome of hypertension and proteinuria is part of a severe systemic inflammatory response that includes leukocyte and endothelial cell activation.

PCT is a polypeptide consisting of 116 aminoacids and is the precursor of calcitonin. Over the last decade, PCT has become increasingly popular as a novel marker of infection in the intensive care unit setting.

The aim of our study was to evaluate changes in serum levels of PCT in pregnancies complicated with mild pre-eclampsia or severe pre-eclampsia and further investigate the correlation with CRP.

Methods: Throughout the study period, 80 pregnant women complicated with mild preeclampsia, 80 pregnant women complicated with severe preeclampsia and 80 healthy pregnant women as a control group, giving a total of 240 pregnant women were enrolled into study.

Results: Both severe pre-eclampsia and mild pre-eclampsia groups showed significantly higher PCT values when compared with control healthy group ($p<0.05$). Also, severe pre-eclampsia group showed significantly higher PCT values when compared with mild pre-eclampsia group ($p<0.05$).

A statistically significant correlation was observed in between presence of pre-eclampsia and procalcitonin positivity ($p<0.05$). And also severity of pre-eclampsia has shown a statistically significant correlation with high values of procalcitonin ($p<0.05$).

Conclusion: Procalcitonin might be a diagnostic marker for investigating women especially with suspected severe preeclampsia.

Keywords*:* Procalcitonin, Pre-eclampsia, inflammation, marker.

INTRODUCTION

Pre-eclampsia is a common and potentially dangerous disorder of human pregnancy. The maternal syndrome of hypertension and proteinuria is part of a severe systemic inflammatory response that includes leukocyte and endothelial cell activation. Although the origins of pre-eclampsia remain unclear, a major cause is the failure to develop an adequate blood supply to the placenta, leading to placental oxidative stress. This results in the excess release of placental factors, such as syncytiotrophoblast debris or soluble fms-like tyrosine kinase-1 (sFlt-1), the soluble receptor for vascular endothelial growth factor (VEGF), into the maternal circulation, where they trigger an inflammatory response and endothelial dysfunction. Alternatively, pre-eclampsia can develop in the presence of a normal placenta in women that are susceptible to systemic inflammation, such as with chronic cardiovascular disease or diabetes [1]. While clinical management of pre-eclampsia doesnot currently include anti-inflamatory agents, current research is focusing on possibility of predicting preeclampsia cases with an inflammation marker, procalcitonin (PCT).

PCT is a polypeptide consisting of 116 aminoacids and is the precursor of calcitonin [2]. The role of PCT in inflammatory conditions, such as sepsis, was first described by Assicot *et al*. [3], who observed a rise in serum PCT levels three to four hours after a single injection of endotoxin, reaching a maximum 24 hours thereafter [4]. The origin of PCT in the inflammatory response is not yet fully understood, but it is believed that PCT is produced in the liver [5] and peripheral mononuclear cells [6], modulated by cytokines and lipopolysaccharides. Over the last decade, PCT has become increasingly popular as a novel marker of infection in the intensive care unit setting. Several studies have underscored its value in a variety of clinical conditions for identifying infectious processes [7-9], characterising the severity of the underlying illness [10, 11], guiding therapy [12-14], and risk satisfaction [15-17]. However, additional studies indicate that PCT may be a cytokine-like mediator of inflammation rather than a simple marker of infection [4, 18].

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High-sensitivity C-reactive protein (hsCRP) has been reported to be increased in many patients with preeclampsia, even in the absence of manifest infection, and it could be used as a severity marker [19].

Therefore, the aim of our study was to evaluate changes in serum levels of PCT in pregnancies complicated with mild pre-eclampsia or severe pre-eclampsia and further investigate the correlation with CRP.

MATERIALS AND METHODS

Patient Population

This study was conducted in between January 2005 and June 2008 at perinatology department of Ege Obstetrics and Gynecology Teaching and Research Hospital. Throughout the study period, 80 pregnant women complicated with mild preeclampsia (proteinuria ≥300 mg/24h, and at least two readings of systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg), 80 pregnant women complicated with severe preeclampsia (proteinuria ≥5 g/24h, and at least two readings of systolic blood pressure ≥160 mmHg and diastolic blood pressure ≥110 mmHg) and 80 healthy pregnant women as a control group, giving a total of 240 pregnant women were enrolled into study. None of these cases suffered from overt inflammatory disease within the past 2 months, nor did they show evidence of cancer, liver abnormalities or hypothyroidism. None of these cases was affected furthermore by chronic viral infections (ie, hepatitis B or C) nor complicated with premature (and/or preterm) rupture of membranes. Criteria used to rule out current infection were body temperature of <38°C and leukocyte count <12.000/mm^3 and use of antibiotic therapy.

All of the cases gave their written informed consent and were enrolled in the study, after approval by local Ethics Committee, performed according to the principles of Declaration of Helsinki.

Blood Sampling and Laboratory Method

Blood samples were drawn after an overnight fast by antecubital venipuncture. Blood was collected directly into siliconized vacuum tubes containing no additives (Becton-Dickinson, Oxford, UK). Blood was centrifuged at 1500Xg for 10 minutes at room temperature, and the serum was seperated, stored in aliquots and kept frozen at -70°C until measurement. Biochemical parameters were measured on the Modular System P (Roche Diagnostics GmbH, Mannheim, Germany), A particle enhanced turbidimetric immunoassay technique was used to determine the CRP level (IMMAGE, Beckman Coulter Inc., Fullerton, CA). A normal CRP value is less than 5 mg/L. The WBC count was performed using the ADVIA 60 counter (Bayer Vİtal GmbH, Leverkusen, Germany). A normal WBC count is less than 12000 /mm^3.

All members of our interdisciplinary team are blinded to the PCT values. All PCT assays were processed at Microbiology laboratory of Infectious Diseases and Microbiology Department of Tepecik Teaching and Research Hospital. PCT samples were centrifuged and immediately frozen and stored at -70°C. Assays were performed in batches at the end of the study period. Each of the assays lasted 1 ½ h. The circulating PCT level was measured by LUMI test PCT (VIDAS BRAHMS, Henningsdorf, Germany). This immunolumimetric assay is based on the reaction of two-antigen specific monoclonal antibodies that bind procalcitonin (as an antigen) to calcitonin and katacalcin segments. The interassay precision of the kit is 6-10%, the lower limit of detection was 0.08 ng/ml, and the normal range for hospital inpatients was found to be <0.5 ng/ml.

Statistical Analysis

We analyzed the comparability of the differences in between the groups by using the ANOVA and post-hoc corrections or with Kruskal Wallis, as appropriate. The Spearman correlation test was used to compare PCT and CRP values. Values were shown as geometric mean and standard error of the mean (SEM). The level of statistical significance was set at $p<0.05$. All statistical analyses were performed with SPSS software, version 11 (SPSS Inc, IL, USA).

RESULTS

Mild pre-eclampsia group has a mean age of 23.01 ±2.3 years and revealed a mean Procalcitonin (PCT) value of 1.45 ± 0.8 ng/mL (range 0.44 – 6.12 ng/mL) and mean C-Reactive Protein (CRP) value of 2.3 ± 0.6 mg/L (range 0.2 – 4.1 mg/L). Severe pre-eclampsia group has a mean age of 24.12 ± 1.2 years and revealed a mean PCT value of 16.25 ± 7.13 ng/mL (2.3 – 191.4 ng/mL) and mean CRP value of 4.9 ± 1.7 mg/L (3.8 – 7.4 mg/L), whereas the control group has a mean age of 24.8 ± 3.6 years with a mean PCT value of 0.09 ± 0.02 ng/mL (<0.08 – 0.44 ng/mL) and a mean CRP value of 0.8 ± 0.15 mg/L (0.52 – 1.95 mg/L).

Table 1: Characteristics of the Cases together with Calculated Mean Values and Statistical Significance

	Mild Pre-Eclampsia	Severe Pre-Eclampsia	Control (Healthy)	
	Mean	Mean	Mean	
Age	23.01	24.12	24.8	p>0.05
Gravida	1.3	1.1	1.1	p>0.05
Parity	0.4	0.2	0.6	p>0.05
Gest.week	33.2	34.3	34.2	p>0.05
WBC	11800	10500	10200	p>0.05
CRP	2.3	4.9	0.8	p<0.05
PCT	1.45	16.25	0.09	p<0.05

The characteristics of the cases were shown on Table **1**. No statistically significant difference was observed in between three groups according to the mean ages (p>0.05), gravida (p>0.05), parity (p>0.05), gestational week (p>0.05), WBC count (p>0.05).

Both severe pre-eclampsia and mild pre-eclampsia groups showed significantly higher PCT values when compared with control healthy group (p<0.05). Also, severe pre-eclampsia group showed significantly higher PCT values when compared with mild pre-eclampsia group (p<0.05).

CRP values of mild pre-eclampsia group and healthy control group revealed no statistically significant difference (p>0.05), however a statistically significant difference was observed in between severe pre-eclampsia group and healthy control group (p<0.05) (but the mean values were still in normal range).

A statistically significant correlation was observed in between presence of pre-eclampsia and procalcitonin positivity (p<0.05). And also severity of pre-eclampsia has shown a statistically significant correlation with high values of procalcitonin (p<0.05).

White blood cell counts revealed no significant differences in between three groups, and were still in normal range (p>0.05).

DISCUSSION

Pre-eclampsia - increased blood pressure and proteinuria appearing after the twentieth week of pregnancy - is a major cause of maternal and neonatal morbidity, leading to iatrogenic prematurity. Several lines of evidence suggest that the disorder is owing to diminished invasion of spiral arteries by trophoblastic cells, followed by reduced perfusion of the fetoplacental unit and oxidative stress. These alterations, in the presence of maternal predisposition, lead to endothelial dysfunction and occurrence of the clinical syndrome of pre-eclampsia (multisystemic lesions). Although the pathophysiology of pre-eclampsia is still unknown, progress has been made during the past 10 yr, and the early identification of at-risk women with the use of biochemical; ultrasonographic; and, more recently, genetic susceptibility markers has been the subject of intense research [20].

The last 10 years has seen a dramatic increase in our understanding of the mechanisms underlying the pregnancy-specific adaptation in cardiovascular function in general and the dramatic changes that occur in uterine artery endothelium in particular to support the growing fetus. The importance of these changes is clear from a number of studies linking restriction of uterine blood flow (UBF) and/or endothelial dysfunction and clinical conditions such as intrauterine growth retardation (IUGR) and/or pre-eclampsia in both humans and animal models. The recent developments that prompts this study are twofold. The first is advances in an understanding of the cell signaling processes that regulate endothelial nitric oxide synthase (eNOS) in particular [21]. The second is the emerging picture that uterine artery (UA) endothelial cell production of nitric oxide (NO) as well as prostacyclin (PGI2) may be as much a consequence of cellular reprogramming at the level of cell signaling as due to tonic stimuli inducing changes in the level of expression of eNOS or the enzymes of the PGI2 biosynthetic pathway (cPLA2, COX-1, PGIS). In reviewing just how we came to this conclusion and outlining the implications of such a finding, we draw mostly on data from ovine or human studies, with reference to other species only where directly relevant [22].

Recombinant PCT inhibits the iNOS-inducing effects of the proinflammatory cytokines TNF-alpha/ IFN-gamma in a dose-dependent manner. This might be a counter-regulatory mechanism directed against the large production of NO and the concomitant systemic hypotension in severe inflammatory processes like severe sepsis and septic shock [23].

Maternal endothelial function is impaired in women who eventually develop pre-eclampsia and it occurs before the development of the clinical syndrome. Furthermore, women with high resistance placental circulation at risk of pre-eclampsia, IUGR, or both have raised concentrations of asymmetric dimethylarginine (ADMA; the endogenous inhibitor of endothelial nitric oxide synthase), which is a potential contributory factor for pre-eclampsia, and is associated with endothelial dysfunction in some women [24].

In other words, preeclampsia is a condition characterized by endothelial cell dysfunction and inflammation and these two events are considered to have crucial role in the pathophysiological mechanism of pre-eclampsia [25].

Endothelial activation and damage occur early during sepsis and play a major role in the pathophysiology of systemic inflammation. Various markers of endothelial activation are increased during sepsis and systemic inflammation, and in most studies, the level of markers such as soluble intercellular adhesion molecule, vascular cell adhesion molecule, and E-selectin correlate well with the severity of inflammation and the course of the disease. However, to date, it remains unclear whether adhesion molecules and coagulation parameters are superior in this respect to interleukin-6 and procalcitonin, as direct comparisons are lacking. In addition, it is evident that markers of endothelial activation and coagulation parameters lack specificity for infection-induced endothelial damage and organ dysfunction [26].

The function and regulation of this protein are quite different from those of the other gene products. Blood concentrations of procalcitonin are increased in systemic inflammation, especially when this is caused by bacterial infection. Studies of its behaviour in patients with bacterial sepsis have led to the proposal that it may be a useful marker of systemic bacterial infection, with greater specificity and sensitivity than acute phase proteins such as C-reactive protein [27].

Although PCT is currently considered a sensitive and specific marker of systemic bacterial infection, we observed that PCT values might be related to the presence and severity of pre-eclampsia in patients without concomitant infections, whereas CRP was not a significant predictor of pre-eclampsia in our study population.

Literature review revealed only one study about the procalcitonin relation with pre-eclampsia which had a limited number of study cases; Montagnana *et al*., also reported a significant relation in between PCT values and the presence and severity of pre-eclampsia [28].

CONCLUSION

Procalcitonin might be a diagnostic marker for investigating women especially with suspected severe preeclampsia, which clinical usefulness might even be superior if a prospective study is conducted from the beginning of the pregnancies and observing the changes in procalcitonin values, if the pregnancy is complicated with pre-eclampsia, subsequently.

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