Procalcitonin As a Vital Tool for Grading Preeclampsia: A Case Control Study in Central India

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ABSTRACT
Aim & Objective: Preeclampsia is a condition comprised of hypertension (>140/90 mm Hg) associated with proteinuria and edema in pregnant women after the 20th gestational week and most frequently near term. It is recognized that chronic inflammation plays important role in the pathogenesis of preeclampsia. The aim of our study was to estimate & assess serum Procalcitonin (PCT) level in pre-eclamptic women and to compare the levels of Procalcitonin in different groups of preeclampsia patients and normal controls. Material & Methods: Total 105 pregnant women during third trimester (28-40 weeks) aged 18 to 35 years were enrolled. 35 patients with mild preeclampsia and 35 with severe preeclampsia were taken as cases. Age matched 35 normotensive pregnant women were taken as control. Subjects were enrolled after applying all inclusion and exclusion criteria and written informed consent were taken. Inflammatory marker Procalcitonin was estimated by enzyme linked immunosorbent assay (ELISA) method using a commercially available kit on Thermofisher ELISA reader & washer. Results: The mean PCT in the control group was 116.8 ±5.8 pg/ml while in mild preeclampsia and severe preeclampsia were 166.70 ± 11.6 and 210.98 ±11.9 pg/ml respectively. The difference was found to be statistically significant (p<0.01), showing a higher PCT in Preeclamptic women in comparison to the control group. Conclusion: From this study, it can be concluded that elevated serum PCT levels are associated with severity of preeclampsia. Therefore early estimation of PCT levels in preeclamptic women may be useful for the proper management of these patients to reduce the morbidity and mortality.

Keywords: Cytokine, Inflammation, Preeclampsia, Procalcitonin (PCT)

INTRODUCTION
Preeclampsia (PE) is defined as hypertension (systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg after 20 weeks of gestation) and proteinuria (≥300 mg in a 24 h urine collection or one dipstick measurement ≥1+) [1]. Severe PE was diagnosed on the basis of diastolic blood pressure ≥110 mmHg or significant proteinuria (dipstick measurement of ≥2+), or the presence of symptoms such as headache, visual disturbances, upper abdominal pain, oliguria, convulsion, elevated serum creatinine, thrombocytopenia, marked liver enzyme elevation, and pulmonary edema[1]. The incidence of preeclampsia is 3-10% globally and 8-10% in India. PE is an important cause of maternal and perinatal mortality affecting 5–7% of pregnant women [2].

The exact pathogenesis of PE is not clear till date [3]. Several studies suggested that toxic combination of...
imbalance of angiogenic factors, hypoxia, impaired immunity and inflammation are the factors responsible for Preeclampsia [4].

In PE, the systemic maternal inflammatory response is enhanced. Several studies have reported higher level of inflammatory cytokine in PE than those with normal pregnancies [5-7].

Recently, several researches have evaluated Procalcitonin (PCT) as an important biochemical marker in PE. It has been used as an indicator of systemic inflammations mainly induced by bacterial infection. [8]. The half-life of PCT is 25–30 hours and rises and decreases more quickly during and after alleviation of infection as compared to other inflammatory markers such as ESR and CRP [9].

Regarding the fact that PE is developed due to exaggerated maternal systemic inflammatory response during pregnancy, so this is used as a predictor for PE [10-12].

PCT (14.5-kDa protein) is the 116 amino acid polypeptide and a precursor of calcitonin (a calcium regulatory hormone). Production of PCT is regulated by the Calc-1 gene, located on chromosome 11. Calc-1 codes for pre PCT, which undergoes proteolytic cleavage of its signal sequence to produce the definitive PCT molecule [13]. Current evidence suggests that PCT might be useful for detecting and evaluating severity of systemic bacterial infections. However, some studies indicate that PCT may be a cytokine-like mediator of inflammation rather than a simple marker of infection.

Our study is mainly focusing on to estimate & assess serum PCT level in preeclamptic women and to compare the levels of PCT in different groups of PE patients and normal controls, so that early diagnosis of such a serious complication of pregnancy, which does not have specific diagnostic marker, would be helpful in preventing morbidities and mortalities related to the disease.

MATERIAL AND METHODS;

This case control study was conducted in Department of Clinical Biochemistry MGM Medical College and M.Y. Hospital Indore after ethical approval. 105 pregnant women during third trimester (28-40 weeks) aged 18 to 35 years were enrolled from the Department of Obstetrics & Gynecology of M.Y. Hospital, Indore. 35 patients with mild preeclampsia and 35 with severe preeclampsia were taken as cases. Age matched 35 normotensive pregnant women were taken as control. Written informed consent was obtained from each selected participants.

The inclusion criteria- Singleton pregnancy, Age 18 to 35 years, Preeclamptic women whose blood pressure was normal during first 20 weeks of gestation, No previous history of hypertension, All the cases were in the third trimester of pregnancy ( > 28 weeks of gestation).

The exclusion criteria- Infection, Chorioamnionitis, Urinary tract infection, Chronic renal or hepatic disorder, Smoking and alcoholism, Diabetes mellitus, Preganacies with multiple fetuses.

Fasting blood sample 5ml was collected by aseptic precautions in clot activator tube. Serum was separated and analyzed for biochemical investigations. Serum PCT level was estimated by sandwich ELISA using a Human PCT ELISA Kit on Thermo Fisher ELISA Reader.

STATISTICAL ANALYSIS-

The data were expressed as mean ± standard deviation. SPSS 20 software version was used for statistical analysis. Unpaired Student t test was applied to compare PCT level between control & cases. P values <0.05 was considered significant

RESULT AND OBSERVATIONS-

The demographic and biochemical profiles of the study subjects are shown in Table 1 & Table 2. Table 1 shows that subjects with preeclampsia had significantly higher level of- systolic blood pressure(157.1 vs 110.7) with p value < 0.05, diastolic blood pressure(99.7 vs 67.3) with p value <0.05, proteinuria(3.98 vs 0.19) with p value <0.01, PCT in pregnant women with severe PE, mild PE, normal pregnant women(210.98 vs 166.70 vs 116.8) respectively with p value <0.01.
### Table 1 - Comparison of Demographic & Clinical profile between cases and controls

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal Pregnant Women (n=35)</th>
<th>Pregnant Women With PE (n=70)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25.6 ± 5.3</td>
<td>26.3 ± 6.2</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Gestational age (week)</td>
<td>36.4 ± 4.1</td>
<td>35.2 ± 2.9</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>31.8 ± 2.6</td>
<td>32.2 ± 2.5</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>110.7 ± 18.5</td>
<td>157.1 ± 26.8</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>67.3 ± 13.6</td>
<td>99.7 ± 16.4</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Proteinuria (gm/day)</td>
<td>0.19 ± 0.09</td>
<td>3.98 ± 1.02</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

### Table 2 - Comparison of Procalcitonin levels between cases and controls.

<table>
<thead>
<tr>
<th>Biochemical Parameter</th>
<th>Normal Pregnant Women (n=35)</th>
<th>Pregnant Women with mild Preeclampsia (n=35)</th>
<th>Pregnant Women with severe Preeclampsia (n=35)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT (pg/ml)</td>
<td>116.8 ± 5.8</td>
<td>166.70 ± 11.6</td>
<td>210.98 ± 11.9</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>
Figure 1- Elevated PCT level (>150pg/ml) in 82.9% of mild Preeclamptic women

Figure 2- Elevated Procalcitonin level (>150pg/ml) in 91.4% severe Preeclamptic women

Figure 3- Serum PCT level in different groups with higher serum PCT level in severe preeclamptic women than mild preeclamptic and normotensive pregnant women
Discussion:

The main findings of our study are as follows:

1) Mild preeclamptic women (n=35) shows elevated serum procalcitonin level than those with normal pregnancy
2) Severe preeclamptic women (n=35) shows more elevated PCT level than mild preeclamptic and normotensive pregnant women.

Preeclampsia is characterized by endothelial cell dysfunction and inflammation and these two events are considered to have a crucial role in the pathophysiological mechanism of preeclampsia.

Redman et al. first proposed that preeclampsia arises as a result of an excessive maternal intravascular inflammatory response to pregnancy, which may occur because either the stimulus or the maternal response is too strong and involves both the innate and the adaptive immune system.

Two decades ago, Greer et al. showed that neutrophil activation is confined to the maternal circulation in pregnancy-induced hypertension, where it may contribute to vascular damage.

Several studies have found a statistically significant increase in macrophages and dendritic cells in preeclamptic placentas compared to placentas from normotensive pregnancies. An increase in the concentration of cytokines molecules capable of recruiting macrophages and dendritic cells has also been found in preeclamptic placentas. This increased presence of cytokines, macrophages, and dendritic cells in preeclamptic placentas supports the hypothesis that an inflammatory milieu presents in women with preeclampsia.

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 preeclampsia in patients without concomitant infections. Some studies indicate that PCT may be a cytokine-like mediator of inflammation.

In this study, we mainly focussed on the possible role of PCT in preeclampsia and found a significant increase of PCT among severe preeclamptic patients as compared to mild preeclamptic and normal pregnancies with p-value (<0.01) as illustrated in (Table 2) and (Figure 3).

Our findings are consistent with studies of Kucukgoz Gulec et al. and Artunc-Ulkumen et al. Montagnana et al. and Can et al. also found higher level of PCT in severe preeclampsia.

Conclusion:- The findings of this study indicated that higher level of PCT in pregnant women with severe PE than those with mild PE and normal pregnancy could potentially explain the exaggerated inflammation in PE. From this study, it can be concluded that elevated serum PCT levels are associated with severity of preeclampsia. Inflammatory pathway playing pivotal roles in the development and progression of preeclampsia & its complications. Therefore estimation of PCT levels in preeclamptic women may be useful for the proper management of these patients to reduce the morbidity and mortality.

References:


