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Maternal circulatory levels of procalcitonin, uric acid, and lipid profile in Early-onset preeclampsia and Late-onset preeclampsia

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***Abstract*---**Aim: To determine the circulatory procalcitonin levels, lipid profile and uric acid levels in patients presenting with preeclampsia and to correlate these with clinical severity of the disease. Methodology: This double blinded case-control study was conducted for two years in department of Obstetrics and Gynecology in collaboration with the department of biochemistry, Government Institute of Medical Sciences, Greater Noida, UP. This study included 80 subjects out of 40 were in group I (Control) and other 40 were in group II (PE patients) admitted in the hospital in third trimester of pregnancy. General demographic and clinical data such as age, gestational week, number of gestation, and BMI were recorded, and

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the results of routine blood cell counts, PCT and other indicators were also obtained. The PE patients were women younger than 40 years old who met the diagnostic criteria for PE in the guidelines for diagnosis and treatment of hypertensive diseases in pregnancy-2014. The healthy pregnant women were between 24 and 40 years old, with a single fetus, normal fetal development, normal liver and kidney function, and without eclampsia, gestational diabetes mellitus, fetal growth restriction, or history of other adverse pregnancy conditions. Results: Both the groups had equal number of subjects (n=40 each) with approximately same mean demographic details like age, weight, height, BMI. Mean gestational age in group I was 33.66 weeks and in group II was 34.55 weeks. In group II, 17 were EOPE 1 and 23 were LOPE 2. In group I, EOC 3 and LOC 4 had 20 subjects each. Mean diastolic and systolic BP were more in group II as compared to group I (94.95 and 150 mmHg vs 74.29 and 109.76 respectively). Mean PCT value in group II was much more than Group I. Group II had 5.63 mg/dl mean uric acid levels while group I had 4.55 mg/dl. HBA1C values were approximately same in both the groups. TLC cells/mm3 were more in number in group II as compared to group I. Cholesterol, HDL was decreased and LDL were found slightly more in Group I as compared to group II. Conclusion: Concerning the clinical and diagnostic importance of PCT, its serum levels can be considered a good diagnostic marker of PE, although PCT cannot be considered a predictive marker of PE onset. Furthermore, PCT emerges as a good prognostic marker of the severity of PE. This study also has confirmed the association between severe preeclampsia and elevated serum uric acid. We recommend a cross-sectional multicentre study to define the reference range of lipid profile in pregnancy as well as the possible role of preeclampsia in lipid metabolism.

***Keywords*---**Preeclampsia, procalcitonin, uric acid, lipid profile.

Introduction

Preeclampsia (PE), a human-pregnancy-specific disease defined as the occurrence of hypertension and significant proteinuria in a previously healthy woman on or after the 20th week of gestation, occurs in about 2–8% of pregnancies [1, 2]. It is the most common medical complication of pregnancy whose incidence has continued to increase worldwide, and It is associated with significant maternal morbidity and mortality, accounting for about 50,000 deaths worldwide annually [3, 4]. Risk factors for preeclampsia include nulliparity, multifetal gestations, previous history of preeclampsia, obesity, diabetes mellitus, vascular and connective tissue disorders like systemic lupus erythematosus and antiphospholipid antibodies, age >35 years at first pregnancy, smoking, and African American race. Most theories on the etiology of preeclampsia suggest that the disease is a cascade triggered by combination of abnormal maternal inflammatory response, endothelial cell activation/damage with deranged hemodynamic milieu, and deranged immunity [5-7].

Procalcitonin (PCT), the prohormone of calcitonin (CT), is a protein that consists of 116 amino acids [8, 9]. During severe inflammation or sepsis the serum levels of PCT rapidly increase (>0·5–1 ng/ml) [10]. For this reason, PCT is now generally accepted as a good predictive and diagnostic marker of the inflammatory process and as an additional tool to guide antibiotic prescribing [10, 11]. In preeclampsia, the systemic maternal inflammatory response is enhanced and characterized by a generalized intravascular inflammatory reaction. According to many studies, PCT plasmalevels are increased in PE and its levels correlate with the severity of the disease [12-14].

Uric acid is the end product of purine metabolism, produced via the action of xanthine oxidase and plays a central role in free radical scavenging, presenting both pro-oxidant and antioxidant properties [15]. During normal pregnancy, serum urate concentration is significantly decreased due to plasma volume expansion, while its clearance is amplified by the increased glomerular filtration rate and the uricosuric effects of estrogen [16]. On the other hand, preeclampsia has been considered as a state of hyperuricemia, mainly due to increased urate tubular reabsorption, stimulated by the presence of relative hypovolemia and the action of angiotensin II [17]. Uric acid excretion is also impaired as a result of lactate competition in the proximal tubule, while its production is magnified by the increased trophoblast turnover [18]. Moreover, it has been assumed that uric acid may have a role in the progression of the disease, since its elevated concentration may inhibit nitric oxide production, leading to inadequate trophoblast invasion and impaired endothelial repair [19].

Endothelial dysfunction, which is central to the pathology of preeclampsia, has also been linked to hyperlipidemia; and abnormal lipid peroxidation in preeclampsia, especially with respect to triglycerides, has been consistently reported in the literature. It is likely that an imbalance between lipid peroxidation and antioxidant mechanisms may impair endothelial function leading to the manifestation of preeclampsia. In the present study, we aimed to determine the circulatory procalcitonin levels, lipid profile and uric acid levels in patients presenting with preeclampsia and to correlate these with clinical severity of the disease.

Materials and Methods

This double blinded case-control study was conducted for two years, in Department of Obstetrics and Gynecology, Government Institute of Medical Sciences, Greater Noida, UP.

Inclusion criteria:
The PE patients were women younger than 40 years old who met the diagnostic criteria for PE in the guidelines for diagnosis and treatment of hypertensive diseases in pregnancy (2014).[12] The healthy pregnant women were between 24 and 40 years old, with a single fetus, normal fetal development, normal liver and kidney function, and without eclampsia, gestational diabetes mellitus, fetal growth restriction, or history of other adverse pregnancy conditions.

Exclusion criteria:
Patients with smoking, alcohol, and drug use were excluded, as were those with medical conditions including chronic hypertension with pregnancy, acute and chronic hepatitis, acute and chronic kidney diseases, cardiovascular and cerebrovascular diseases, and endocrine and blood system diseases. Patients with other pregnancy complications were excluded.

Methodology

This study included 80 subjects out of 40 were in group I (Control) and other 40 were in group II (PE patients) admitted in the hospital in third trimester of pregnancy. General demographic and clinical data such as age, gestational week, number of gestation, and BMI were recorded, and the results of routine blood cell counts (Automated cell counter for CBC), PCT (Architect i1000SR immunoassay analyser) and other indicators like uric acid and lipid profile (Fully automated analyser Selectra Pro XL) were obtained.

Results

Both the groups had equal number of subjects (n=40 each) with approximately same mean demographic details like age, weight, height, BMI. Mean gestational age in group I was 33.66 weeks and in group II was 34.55 weeks. In group II, 17 were EOPE 1 and 23 were LOPE 2. In group I, EOC 3 and LOC 4 had 20 subjects each. In control group, urinary protein (dipstick) was present in all subjects but not in PE patients group.

Table 1: Demographic details and physical characteristics of the patients

Variables	Group I (Control)	Group II (PE patients)
	N=40	N=40
EOPE 1	Nil	17
LOPE 2	Nil	23
EOC 3	20	Nil
LOC 4	20	Nil
Gestational age in weeks	33.66	34.55
Urinary Protein (Dipstick)	Absent in all	Present in all
Mean age (in years)	25.27	26
Mean weight (in Kg)	151.85	152
Mean height (in cms)	56.07	58
Mean BMI	24.90	25.8

Mean diastolic and systolic BP were more in group II as compared to group I (94.95 and 150 mmHg vs 74.29 and 109.76 respectively). Mean PCT value in group II was much more than Group I. Group II had 5.63 mg/dl mean uric acid levels while group I had 4.55 mg/dl. HBA1C values were approximately same in both the groups. TLC cells/mm3 were more in number in group II as compared to group I. Cholesterol, HDL was decreased and LDL were found slightly more in Group I as compared to group II.

Table 2: Laboratory parameters like BP, blood coagulation tests, lipid profile, PCT and routine blood cell counts

Variables (Mean values)	Group I (Control)	Group II (PE patients)
Systolic BP (mmhg)	109.76	150.00
Diastolic BP (mmhg)	74.29	94.95
PCT	0.055	0.57
Uric acid (mg/dl)	4.55	5.63
HbA1C	4.78	5.01
RBS/PP (mg/dl)	83.35	98
Cholesterol (mg/dl)	250.41	216.92
TGL (mg/dl)	264.02	249.67
HDL (mg/dl)	95.41	56
LDL (mg/dl)	149.05	125
HB (gm/dl)	10.43	9.77
TLC (cells/mm3)	11861.49	13624.78

Discussion

Vascular endothelial injury underlies the pathophysiological changes in PE patients [20]. Placental and immunologic abnormalities lead to the release of inflammatory cytokines in PE patients. Inflammatory factors cause inflammatory reactions, vascular endothelial injury, and exposure of collagen and tissue factors under the endothelium, leading to a series of changes in the coagulation, anticoagulation, and fibrinolytic systems, which then affect other systems [21, 22], leading to fetal death in utero, dysontogenesis, and other adverse obstetrical outcomes. The commonly used laboratory tests of coagulation function in clinical practice include routine blood cell counts, coagulation factors, plasma fibrin degradation products (FDP), antithrombin (AT), and other indicators of coagulation, anticoagulation, and fibrinolytic functions.[23, 24].

PCT is produced from the (calcitonin-related polypeptide alpha-1 (CALC-1) gene located on chromosome 11 (11p15.2), containing six exons. The mRNA product is known as pre-PCT, which is further cleaved to generate the PCT (116 amino acid). Finally, this protein is cleaved into three distinct molecules: active CT (32 amino acid), katacalcitonin (21 amino acid) and N-terminal PCT (57 amino acid) [25]. Normally, the CALC-1 gene in thyroid C cells is induced by elevated calcium level, glucocorticoid, calcitonin gene-related peptide (CGRP), glucagon, gastrin or β-adrenergic stimulations [25, 26]; almost all the PCT formed in thyroid C cells is converted to CT, so that no PCT is released into the circulation [26]. Hence, the PCT level in healthy subjects is very low (<0·05 ng/ml) [27].

Increased PCT levels induce proinflammatory cytokine production that stimulates PCT release which, in turn, triggers the production of PCT itself, causing a positive loop of PCT secretion [27]. Another role that PCT could play in PE pathogenesis is connected with its cytotoxic activity on hepatocytes and endothelium [28, 29]. Indeed, it is well known that peculiar characteristics of PE are endothelial dysfunction and liver damage [30]. Regarding the local role of the

PCT at the fetal–maternal interface in PE, Agostinis et al. detected a strong increase in PCT mRNA expression in PE compared to normal placenta [31].

A recent Chinese study, aimed to establish reference intervals for PCT in healthy pregnant women in the Chinese population, indicated that the serum PCT levels are significantly higher in pregnant versus nonpregnant women, and this increase is particularly evident postpartum [32]. These observations can be justified by the placental production of PCT, due to the physiological synthesis by trophoblast and stromal cell of the decidua, as demonstrated by Agostinis and colleagues in a recent article [31]. A lot of difference was found in PCT values in both the groups in our study. PCT values of PE patients were much higher than control group.

Uric acid levels have been consistently reported to be elevated in preeclampsia with highest levels seen to mirror the severity of the condition [32, 33]. Our results confirmed this observation with half of the patients with severe preeclampsia already having abnormal serum uric acid levels at the time of diagnosis. Serum uric acid levels have been employed as discriminatory to diagnosis of severe preeclampsia because abnormal levels may predate proteinuria by several weeks [32-34].

Conclusion

Concerning the clinical and diagnostic importance of PCT, its serum levels can be considered a good diagnostic marker of PE, although PCT cannot be considered a predictive marker of PE onset. Furthermore, PCT emerges as a good prognostic marker of the severity of PE. This study also has confirmed the association between severe preeclampsia and elevated serum uric acid. We recommend a cross-sectional multicentre study to define the reference range of lipid profile in pregnancy as well as the possible role of preeclampsia in lipid metabolism.

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