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Serum Endoglin and Uric acid in Preeclampsia

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Abstract

Background: Pre-eclampsia (PE), a pregnancy-specific syndrome characterized by new onset hypertension and proteinuria, is a considerable obstetric problem and a significant source of maternal and neonatal morbidity and mortality. Endoglin is a cell-surface co-receptor of transforming growth factor TGF-βI and TGF-β3. sEng sequesters TGF-β1 and block the binding of TGF-β 1 to its receptors and thus impairing the downstream signaling including the effects on activation of endothelial nitric oxide synthase (Enos) and vasodilation. homeostasis. The increase in serum uric acid levels may be related to decreased uric acid excretion in preeclamptic pregnancies.

The increased oxidative stress and the formation of reactive oxygen species were proposed as other contributing sources of the hyperuricemia observed in preeclampsia. The aim of this study was to estimate the serum level of endoglin and uric acid in preeclampsia and assess whether there is any association between them.

Method: A case-control study conducted in the Department of Biochemistry, in collaboration with Department of Obstetrics and Gynaecology, Regional Institute of Medical Sciences (RIMS), Imphal, Manipur. A total number of 60 subjects admitted in Antenatal Ward (RIMS), participated in the study out of which 30 were cases (preeclamptic women) and 30 were controls (healthy normotensive pregnant women).

Results: Mean±SD of serum endoglin in cases was higher at 14.28±4.09 ng/ml compared to controls was 7.30 ± 1.12 ng/ml with a statistically significant (p = 0.000). The mean level of uric acid in cases (6.36±0.85) mg% was higher than controls (4.24±0.63) mg%. There was positive correlation between serum endoglin and serum uric acid among the cases with (r= .552) which found to be statistically significant (p=0.002).

Conclusion: Serum endoglin and uric acid can be used as diagnostic biomarkers for identifying women at risk of preeclampsia and as a predictor of the disease severity.

Keywords: Preeclampsia, endoglin, uric acid, hyper uricemia, pregnancy induced hyper tension

Introduction

Pre-eclampsia (PE), a pregnancy-specific syndrome characterized by new onset hypertension and proteinuria, is a considerable obstetric problem and a significant source of maternal and neonatal morbidity and mortality. Preeclampsia develops during second half of pregnancy and remits after delivery or termination of the pregnancy, suggesting that the placenta is a central culprit in the disease.[1]

It is diagnosed as blood pressure (BP) of ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with previously normal blood pressure and proteinuria (≥ 300 mg per 24 hour urine collection or ≥ +1 by dipstick method); in the absence of proteinuria, new onset of hyper tension with other multisystem symptoms indicative of preeclampsia such as throm Bo cytopenia, renal insufficiency, impaired liver function, pulmonary edema or cerebral or visual symptoms.[2]

The incidence of preeclampsia is about 5-7% of all pregnancies.[3] According to the World Health Organization(WHO) the incidence of preeclampsia is seven times higher in developing countries (2.8% of live births) than in developed countries (0.4%).[4]

Endoglin is a 180-kDa homodimeric transmembrane glycoprotein consisting of 633 amino acids and composed of two disulfide-linked subunits of 95 kDa each.[5]

Endoglin is a cell-surface co-receptor of transforming growth factor TGF-βI and TGF-β3. TGF-β is a pleiotropic cytokine which regulate cellular proliferation, differentiation, migration and adhesion and is essential for vascular homeostasis.[6] Endoglin is highly expressed on endothelial cells, syncytiotrophoblasts, endometrial stromal cells, monocytes and hematopoietic stem cells.[7]

sEng (soluble circulating form) is produced by the proteocleavage of the placental-membrane bound form (mEng) by the action of membrane bound matrix metallo proteinase-14 (MMT-14) in the extracellular domain. It is an anti- angiogenic factor, which was first implicated in the pathogenesis of preeclampsia and HELLP syndrome.[8]

sEng sequesters TGF-β1 and block the binding of TGF-β 1 to its receptors and thus impairing the downstream signaling including the effects on activation of endothelial nitric oxide synthase (eNOS) and vasodilation.[9]

Studies have shown that endoglin plays an important role in the pathogenesis of preeclampsia.

Uric acid is formed when the body breaks down substances called purines. The increase in serum uric acid levels may be related to decreased uric acid excretion in preeclamptic pregnancies.[10]

The increased oxidative stress and the formation of reactive oxygen species were proposed as other contributing sources of the hyperuricemia observed in preeclampsia. On the other hand, due to the uric acid interaction with proinflammatory cytokines, increased levels of uric acid in the plasma of patients with preeclampsia may indicate a direct contribution to the pathophysiology of this syndrome by its ability to promote inflammation.[11] A number of studies recently proposed that higher levels of uric acid are involved in the pathogenesis of preeclampsia by contributing to the generalised maternal endothelial activation and exaggerated inflammation observed.[12] So, this study was planned to evaluate the serum level of endoglin and uric acid in preeclampsia and assess whether there is any association between them.

Materials and Methods

Study design: Case-control study

Study setting: The study was conducted in the Department of Biochemistry, in collaboration with Department of Obstetrics and Gynaecology, Regional Institute of Medical Sciences (RIMS), Imphal, Manipur.

Study duration: The study was carried out for a period of period of 24 months from October 2018 to September 2020.

Study population: A total number of 60 subjects admitted in Antenatal Ward (RIMS), participated in the study out of which 30 were cases (preeclamptic women) and 30 were controls (healthy normotensive pregnant women).

Inclusion criteria: 1. Patients considered as cases were preeclamptic women aged 18 years and above, admitted in Antenatal Ward (RIMS) and willing to participate in the study.

2. Participants considered as controls were normotensive pregnant women with no proteinuria, admitted in Antenatal Ward (RIMS).

Exclusion criteria: Patients who suffered from the following illness which might influence the serum endoglin level independently were excluded: Chronic hypertension**,** diabetes mellitus**,** multiple pregnancy**,** renal disease**,** gestational diabetes mellitus**,** smokers**,** alcohol consumers and neoplastic disease.

Statistical Analysis: Categorical variables were summarized as frequency and percentage and were analyzed using Chi square test. Continuous variables were summarized as mean and standard deviation and were analyzed using independent sample t test.

Results

Table-1 shows that the maximum number of cases i.e., 11 (36.7%) were in the age group of >35-40 years. This was followed by 7(23.3%) cases in the age group of >30-35 years .6 cases (20.0%) were in the age group of >25-30 years. 5 (16.7%) and 1 (3.3%) of cases were in the age group of >20-25 years and 18-20 years respectively. In the control group, the maximum number 9(30.0%) were in the age group >30-35 years followed by 7 (23.3%) and 6 (20.0%) in the age group of > 35-40 years and >20-25 years respectively. 5 (16.7%) and 3 (10.0%) of controls were in the age group of >25-30 years and 18-20 years respectively. The mean±SD of age in cases and controls were found to be 29.93±5.9 years and 29.07±3.9 years respectively. The difference was statistically insignificant (p=0.50) which means the cases and controls were comparable with respect to age.

Table-2 shows that the mean ± SD of systolic blood pressure in cases was 160.13±10.67 mmHg whereas in controls it was found to be 120.20±12.19 mmHg. Mean±SD of diastolic blood pressure in cases was 102.50±6.4 mmHg whereas in controls it was found to be 75.97±9.8 mmHg. The difference was found to be statistically significant (p=0.000).

Table-3 shows the mean±SD of serum endoglin in cases was 14.28±4.09 ng/ml and controls was 7.30 ± 1.12 ng/ml. Independent T test was used for comparing the values. It was found to be higher in cases as compared to controls and the difference was found to be statistically significant (p = 0.000).

Table-4 shows the correlation between serum endoglin and systolic blood pressure (SBP) and diastolic blood pressure (DBP) among the cases. Pearson correlation coefficient ‘r’ was applied and it was found to be positively correlated for both SBP and DBP with (r=0.819), (r=.861) respectively and the findings was statistically significant (p= 0.000).

Table-5 shows that the mean level of uric acid in cases (6.36±0.85) mg% was higher than controls (4.24±0.63) mg%.

Table-6 shows the correlation between serum endoglin and serum uric acid among the cases. pearsons correlation coefficient 'r" was applied and it was found to be positively correlated (r= .552) and was found to be statistically significant (p=0.002)

Table 1: Age distribution of the respondents.

Age in years	Cases N (%)	Controls N (%)	p-value
18-20	1 (3.3)	3 (10.0)	0.50
>20-25	5 (16.7)	6 (20.0)	
>25-30	6 (20.0)	5 (16.7)	
>30-35	7 (23.3)	9 (30.0)	
>35-40	11 (36.7)	7 (23.3)	
Age (Mean ±SD)	29.93 ±5.9	29.07±3.9	

Table 2: Comparison of blood pressure between cases and controls.

Blood pressure (mmHg)	Cases (mean ±SD)	Controls (mean±SD)	P-value
Systolic	160.13 ±10.67	120.20 ± 12.19	.000
Diastolic	102.50± 6.4	75.97 ± 9.8	.000

Table 3: Comparison of serum Endoglin between cases and controls.

Study groups (N)	Serum endoglin (ng/ml) Mean ± SD	p-value
Cases (30)	14.28 ± 4.09	0.000
Controls (30)	7.30 ± 1.12	

Table 4: Correlation between serum endoglin with systolic blood pressure (SBP) and diastolic blood pressure (DBP) among cases.

Parameters	Pearson correlation (r)	p- value
SBP	.819**	0.000
DBP	.861**	0.000

**Correlation is significant at the 0.01 level (2-tailed).

Table 5: Comparison of Uric Acid between cases and controls.

Study groups (N)	Serum Uric acid (mg%) Mean ± SD	p-value
Cases (30)	6.36±0.85	0.000
Controls (30)	4.24±0.63	

Table 6: Correlation between serum endoglin and serum uric among the cases.

Parameter	Pearson correlation (r)	p – value
Uric acid	.552**	.002

Discussion

In the present study, it was evident from table-1 that maximum number of preeclamptic cases was in the age group of 35 years and above. In this age group, there were 11 cases out of 30 cases. The mean ± SD value of age in cases were found to be 29.93±5.9 years whereas the mean value of age in controls was found to be 29.07±3.9 years and the difference was found to be statistically insignificant (p=0.50) which showed that the studied groups were comparable with respect to age. The finding was supported by the study conducted by Chan TF et al[13], who found out in their study that the incidence of preeclampsia and eclampsia in 20-24 years of age group was the lowest. The relative risk of preeclampsia increased incrementally with the increase in age, as follows: age<20 years, 1.02-fold; 25-29, 1.35-fold; 30 - 34 years, 1.79-fold; 35-39 years, 2.99-fold and ≥ 40 years, 5.13-fold. They concluded that advanced maternal age was associated with increased risk of preeclampsia. Table-2 showed that SBP, DBP were found to be significantly higher in the cases than the controls. The mean±SD of systolic blood pressure in the cases and controls was found to be 160.13±10.67 mmHg and 120.20±12.19 mmHg respectively. The mean±SD of diastolic blood pressure in cases and controls was found

to be 102.50±6.40mmHg and 75.97±9.80 mmHg respectively. A study by Tabassum H et al[14] among Riyadh population has shown that the blood pressure and BMI were higher in cases when compared to controls group and the mean values of SBP, DBP and BMI were 167.0mmHg, 98.51 mmHg and 35.12 kg/m^2 respectively in cases group.

It was evident from the Table 3 that the mean±SD of endoglin level among the cases was 14.28±4.09 ng/ml whereas among the controls it was 7.30±1.12 ng/ml. It was observed that the values of serum endoglin levels in cases were two-fold higher as compared to controls. The findings were supported by the results of the study by Sachan R et al[15] who compared serum endoglin level between healthy normotensive pregnant women and preeclamptic women including eclampsia. They found that the mean value of serum endoglin in severe preeclampsia was 14.94 ± 0.89 ng/ml which was seven times higher than the mean value of serum endoglin in controls, i.e 2.08±0.56 ng/ml. The exact pathophysiology of preeclampsia is unknown but generalised endothelial dysfunction with systemic inflammatory response (SIRs) is thought to be the final common pathway that leads to maternal signs of preeclampsia. Many proangiogenic molecules such as placental growth factor, and vascular endothelial growth factor (VEGF) and anti-angiogenic factors such as fms like tyrosine kinase 1 (sFIt-1) and soluble endoglin are involved in placental vascular development.[8] Soluble endoglin rises during normal as well as in preeclamptic pregnancy. The rise in preeclampsia is much higher. Placental endoglin is upregulated in preeclampsia which result in excess secretion of soluble endoglin in the maternal circulation.[16] This might be responsible for endothelial dysfunction and clinical signs of preeclampsia.

It was also found that there was a strong positive correlation between blood pressure i.e both systolic and diastolic blood pressure and serum endoglin level among the cases and the findings were found to be statistically significant (Table-4). Similarly, Sachan R et al[15] observed the strong positive correlation of SBP and DBP with serum endoglin level (r=0.928 for SBP and r = 0.916 for DBP). Elhawary TM et al[17] also revealed a positive correlation of sEng level with SBP and DBP. This positive correlation can be explained by the fact that serum endoglin block the TGF-β1 mediated activation of endothelial nitric oxide synthase (eNOS) leading inhibition of NOS-dependent vasodilation. It acts by antagonizing, TGF-β, an angiogenic growth factor, which is important in mediating nitric oxide-dependent vasodilation and responsible for keeping the lining of blood vessel healthy. Due to this antagonistic effect cell lining of the blood vessels begin to sicken and die, and this change is responsible for the increase in blood pressure and proteinuria.[18] It is well known fact that severity of preeclampsia increases with increase in BP. Since endoglin levels were strongly correlated with BP, its value also increased with increasing severity of preeclampsia. Thus, the diagnostic ability of clinical sign like BP and a biochemical marker like endoglin levels could complement each other for the diagnosis of preeclampsia.

The mean±SD of serum uric acid in cases was 6.36±0.85mg% which found to be higher than value in controls i.e 4.24±0.63 mg% as shown in table-5. Table-6 shows the correlation between serum endoglin and serum uric acid among the cases. pearsons correlation co efficient ‘r” was applied and it was found to be positively correlated (r= .552) and was found to be statistically significant (p=0.002). This is in accordance to Hasina A et al[19] who found out in their study that the levels of uric

acid was on the higher side in preeclamptic cases. They concluded that elevated serum uric acid level have been interpreted to act as an important cofactor involved in the pathogenesis and manifestation of preeclampsia disorder.[20] It has been proposed recently that increased oxidative stress and formation of reactive oxygen species are another contributing source of hyperuricemia noted in pre-eclampsia.[21] Uric acid possessing water soluble or hydrophilic antioxidant characteristics, may delay or inhibit cellar damage mainly through the free radical scavenging property, it also presents strong antioxidant activity towards reactive oxygen species in aqueous phase. Uric acid may function as a marker of oxidative stress tissue injury dysfunction. Elevated serum uric acid concentrations predict the development of hypertension. Studies showed that uric acid and its level increases once the disease manifests and plasma levels of uric acid may often correlate with disease severity.[22] Women with severe or early onset preeclampsia typically have higher blood pressures and more severe proteinuria.[23] Given that uric acid is a marker of renal dysfunction and therefore proteinuria, the higher levels of uric acid in women with more severe forms of preeclampsia may reflect the severity of renal dysfunction. Lower serum levels of uric acid in women with preeclampsia at presentation has been reported to be linked to the prolongation of pregnancy for more than one week compared with higher serum levels of uric acid at presentation of preeclampsia.[24] Monitoring the serum uric acid levels, we were able to identify a serum uric acid value that could be used to differentiate hypertensive disease. Hence monitoring of plasma uric acid level in those with preeclampsia will help to predict those women that will develop eclampsia. Elevated serum uric acid level has also been interpreted to act as an important cofactor involved in the pathogenesis and manifestation of pre-eclampsia disorder.

Conclusion

This study shows that the level of serum endoglin and serum uric acid were found to be significantly higher in preeclamptic women compared to normal pregnant women. Serum endoglin level was found to be positively correlated with blood pressure and uric acid among the preeclamptic women which was highly significant.

With the increase in serum endoglin and uric acid more adverse pregnancy outcomes were observed. Thus, it can be concluded that Serum endoglin and uric acid can be used as diagnostic biomarkers for identifying women at risk of preeclampsia and as a predictor of the disease severity. However further study with large population may be required to fully assess the diagnostic value of serum Endoglin as well as serum Uric acid in preeclampsia.

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