Original Article

Diagnostic and prognostic significance of serum soluble endoglin levels in preeclampsia and eclampsia

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Abstract

Background: Preeclampsia is a multisystem disorder of unknown etiology that affects 4–5% of all pregnancies. The aim of the study was to evaluate the diagnostic accuracy of serum soluble endoglin (sEng) in preeclampsia and eclampsia and also to evaluate its prognostic significance.

Materials and Methods: This prospective case–control study carried out over a period of 1 year in the Department of Obstetrics and Gynaecology, King George Medical University, Lucknow. After written informed consent and ethical clearance, total 90 subjects were enrolled. Among them, 30 subjects of eclampsia, 15 of nonsevere preeclampsia, 15 of severe preeclampsia served as cases, and 30 healthy pregnant normotensive women served as controls. Levels were estimated by enzyme-linked immunosorbent assay technique in both cases and controls.

Results: Mean level was highest in eclampsia group (14.96 ± 1.96 ng/mL) and lowest in controls (2.08 ± 0.56 ng/mL). At cut-off value of sEng levels of ≥6.26 ng/mL, it was found to be 100% sensitive and 100% specific for the diagnosis of preeclampsia (area under curve =1) at 95% confidence interval. sEng levels were strongly correlated with systolic (r = 0.928) and diastolic blood pressure (r = 0.916), serum lactate dehydrogenase (r = 0.791) and serum uric acid (r = 0.722). All four maternal deaths were reported within eclampsia group, in whom the mean sEng level was significantly higher (17.84 ± 0.22) as compared to other subjects (9.50 ± 5.80).

Conclusion: sEng is a novel marker for diagnosis of preeclampsia, and it can also be used as a prognostic marker to predict the severity of preeclampsia.

Key Words: Eclampsia, endoglin, preeclampsia

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INTRODUCTION

Incidence of hypertensive disorders of pregnancy (HDP) is 5.38%, preeclampsia 44%, eclampsia 40%, and HELLP syndrome (7%) comprise HDP.[1] Preeclampsia is characterized by hypertension and proteinuria after 20 weeks of gestation. Preeclampsia complicates 3–5% of pregnancies and causes substantial neonatal mortality and morbidity.[2,3] Diagnosis of preeclampsia relies on two nonspecific signs of the disease, progressive proteinuria, and hypertension. The diagnostic value of these

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two classical features is limited and is not useful when women have preexisting hypertension and/or proteinuria (e.g., chronic renal disease).[4] The incidence of eclampsia is 0.3–0.9%, and it has a maternal mortality rate of 0.5–10.0%.[5]

Some novel soluble angiogenic factors are identified that are related to the pathogenesis of the disease.[6] These factors include circulating antiangiogenic proteins such as soluble fms-like tyrosine kinase 1 (sFlt-1) and serum soluble endoglin (sEng) and proangiogenic protein such as placental growth factor and vascular endothelial growth factor (VEGF).[7,8] sEng is an antiangiogenic factor with 180 kD, type I membrane glycoprotein located on the vascular endothelial cell surface. It is the part of the transforming growth factor beta (TGF-β) receptor complex.[9] This might be responsible for endothelial dysfunction and clinical signs of sEng inhibit endothelial function *in vitro* and administration of sEng induces hypertension *in vivo*. The combined administration of sEng and serum VEGF receptor 1 (VEGFR-1) (antiangiogenic factor) to pregnant rats induces hypertension, proteinuria, and fetal growth restriction.[9] sEng is produced by the proteolytic cleaving action of matrix metalloproteinase-14 in the extracellular domain.[9,10] Placental endoglin is upregulated in preeclampsia releasing sEng into the maternal circulation. It antagonizes an angiogenic and vasodilator molecule known as TGF-β1 which is important for angiogenesis and responsible for keeping the lining of blood vessels 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 (BP) and proteinuria.[11] Thus, this study was performed to determine the levels of sEng in women with normal pregnancy, preeclampsia, and eclampsia and to assess the diagnostic accuracy of sEng in preeclampsia. We also evaluated its correlation with severity of disease thus assessing its prognostic significance in preeclampsia and eclampsia.

MATERIALS AND METHODS

This was a prospective case–control study carried out over a period of 1 year (from August 2013 to July 2014) in the Department of Obstetrics and Gynaecology, in collaboration with Pathology and Medicine, King George Medical University, Lucknow. After written informed consent and ethical clearance from Institutional Ethics Committee. A total of 950 pregnant women were screened from antenatal clinic over a period of 1 year, 69 of whom diagnosed with a hypertensive disorder of pregnancy and enrolled in our study, and nine were lost to follow-up. Analysis was therefore carried out in 60 cases. 30 healthy normotensive pregnant women who remain normotensive throughout the pregnancy were enrolled as controls. Subjects were randomized into four groups as per computer generated randomization (Group I control group, Group IIa nonsevere preeclampsia, IIb severe preeclampsia, and III eclampsia). Women with preexisting multiple pregnancy, chronic kidney disease, hypertension, liver disease, collagen vascular disease, diabetes, major fetal anomaly, history of smoking, alcohol intake, cardiovascular disease, neoplastic pathology, and women not willing to take part in the study were excluded. Among participants, 30 subjects were cases of eclampsia, 15 of nonsevere preeclampsia, 15 of severe preeclampsia, and 30 healthy pregnant normotensive women served as controls at a gestational age of 20–40 weeks. This control group was well matched with the case for maternal age, prepregnancy body mass index, and gestational age. Demographic characteristics including gestational age, BP on admission, biochemical parameters including serum uric acid, serum lactate dehydrogenase (LDH), and 24 h urinary protein excretion were recorded.

BP was monitored every four hourly since the time of admission, and this monitoring was continued up to 48 h after delivery.

BP was measured by mercury sphygmomanometer in patients with preeclampsia and eclampsia in right arm in supine position and Korotkoff V sounds were taken for measurement of diastolic BP (DBP).

The investigations were carried out in accredited lab. 5 ml of venous blood sample was collected from cases (after the development of disease) and controls and stored at 4°C. Samples were centrifuged at 6000 rpm and frozen at −20°C until assay. Quantitative measurement of sEng was carried out by enzyme-linked immunosorbent assay (ELISA) technique by using Sandwich ELISA Kit (USCN Life Science Inc.) according to the protocol. Urinary protein estimation was carried out by sulfosalicylic acid test, and uric acid estimation was carried out by nephelometry. Proteinuria was defined as 24 h urinary protein excretion of ≥300 mg.

Subgroups were defined as per National High BP Education Program working group (2000). "Mild or nonsevere preeclampsia" was defined as BP ≥140/90 mmHg, but <160/110 mmHg with proteinuria ≥300 mg/24 h. "Severe preeclampsia" was defined as the presence of BP ≥160/110 mmHg with urinary protein excretion ≥2.0 g/24 h or any of these, oliguria <400 ml/urine/24 h, visual disturbances,

serum creatinine ≥1.2 mg/dL, platelet <100,000/mm^3, and microangiopathic hemolysis. Urine output was measured by catheterization and visual disturbances were examined by fundoscopy (ophthalmoscope) serum creatinine measured by Jaffe's method; microangiopathic hemolysis was assessed by general blood picture. "Eclampsia" was defined as the occurrence of new onset grand mall seizure in patient with preeclampsia.

Strict BP and labor monitoring was done. All patients were followed-up to 6 weeks postpartum. Adverse maternal outcome in forms of complications like postpartum hemorrhage abruption, cerebrovascular accident, and maternal deaths were evaluated.

Data were collected and analyzed. The statistical analysis was done using SPSS version 15.0 software. The categorical data were described as *n* (%), whereas continuous variable as a mean ± standard deviation. The ANOVA test was used to compare within the groups and between the group variances among the study groups. Receiver operator characteristic (ROC) analysis was used to determine the optimum cut-off value to evaluate the diagnostic accuracy. A $P < 0.01$ was considered statistically significant.

RESULTS

A total of 90 pregnant women were enrolled in the study. Out of these 60 served as cases and 30 served as controls.15 women of nonsevere preeclampsia, 15 women with severe preeclampsia and 30 women with eclampsia constituted the cases.

The mean age of the controls was 25.37 ± 2.85 years, 25.93 ± 4.51 years in nonsevere preeclampsia, 27.47 ± 5.34 years in severe preeclampsia, and 25.53 ± 4.26 years for eclampsia ($P = 0.408$) [Table 1]. No statistical significant difference was observed in mean age of patients in different groups. All the subjects enrolled were matched for age and parity among the groups. Most of the women (52/90) enrolled in the study were primigravida. Most of the healthy pregnant women and nonsevere preeclampsia (96.7%, 66.67%) respectively belong to middle socioeconomic status.

On the other hand in eclampsia (86.67%) and severe preeclampsia group (53.33%), total 34 out of 45 cases were belonged to lower socioeconomic status. This difference was statistically significant ($P < 0.001$) [Table 1].

As shown in Figure 1 after estimation of sEng levels among various groups, its values were 2.08 ± 0.56 ng/mL in controls, 10.21 ± 0.86 ng/mL in nonsevere preeclampsia group, 14.94 ± 0.89 ng/mL in severe preeclampsia group, and 14.96 ± 1.96 ng/mL in eclampsia group ($P < 0.001$). Mean sEng levels were highest in eclamptic women and lowest in controls. This difference was statistically significant ($P < 0.001$) [Figure 1].

Among the cases, the mean sEng level was lowest in nonsevere preeclampsia group and maximum in

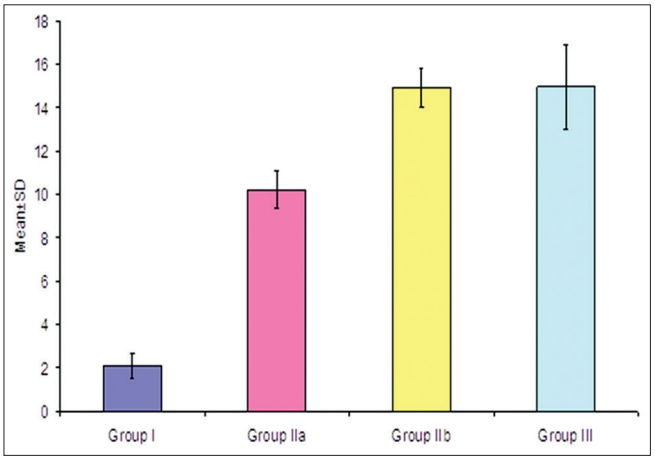

Figure 1: Comparison of mean serum soluble endoglin levels in different study groups (control - 2.08 ± 0.56 ng/mL, nonsevere preeclampsia - 10.21 ± 0.86 ng/mL, severe preeclampsia - 14.94 ± 0.89 ng/mL, eclampsia - 14.96 ± 1.96 ng/mL, $P < 0.001$)

Table 1: Demographic profile of the subjects (prognostic significance of serum endoglin)

Characteristics	Control (*n*=30) (%)	Nonsevere preeclampsia (*n*=15) (%)	Severe preeclampsia (*n*=15) (%)	Eclampsia (*n*=30) (%)	*P*
Age (years)	25.37±2.85	25.93±4.51	27.47±5.34	25.53±4.26	0.408
Domicile					
Rural	8 (26.67)	2 (13.3)	7 (46.67)	15 (50)	0.016
Urban	22 (73.33)	13 (86.67)	8 (53.33)	15 (50)	
Socioeconomic status					
High	1 (3.33)	1 (6.67)	1 (6.67)	0 (0.00)	<0.001
Low	0 (0.0)	4 (26.67)	8 (53.33)	26 (86.67)	
Middle	29 (96.7)	10 (66.67)	6 (40)	4 (13.33)	
Parity					
Primigravida	17 (56.67)	8 (53.33)	7 (46.67)	20 (66.67)	0.845 NS
Multi gravid	13 (43.33)	7 (46.67)	8 (53.53)	10 (33.33)	

Intergroup difference in parity was NS. NS: Not significant

eclampsia group ($P < 0.001$). sEng increased with the progression of disease from nonsevere preeclampsia to severe preeclampsia and eclampsia. The difference of sEng levels among nonsevere and severe preeclampsia group was statistically significant ($P < 0.001$). However, no statistically significant difference was observed for sEng levels between severe preeclampsia group and eclampsia group ($P < 0.0981$) [Table 2].

After ROC curve analysis, at the cut-off value of sEng level of ≥6.26 ng/mL, it was found to be 100% sensitive and 100% specific for the diagnosis of preeclampsia (area under the curve [AUC] =1) at 95% confidence interval (CI) [Figure 2].

sEng levels were strongly correlated with systolic ($r = 0.928$) and DBP ($r = 0.916$) among cases and it was statistically significant ($P < 0.001$) [Figure 3]. It is a well-known fact that severity of preeclampsia increases with increase in BP. Since sEng levels were strongly correlated with BP ($r = 0.928$) for SBP and $r = 0.916$ for DBP, its value also increased after increasing severity of preeclampsia ($P < 0.001$) [Figure 3]. Thus, the diagnostic ability of clinical sign like BP and a biochemical marker like sEng levels could complement each other for the diagnosis of preeclampsia.

Serum LDH and serum uric acid are well-established laboratory markers for assessing the severity of preeclampsia. In our study, we found strong correlation of sEng with serum LDH ($r = 0.791$) and serum uric acid ($r = 0.722$) among the cases. Two-tailed significance test was also indicate that this correlation with sEng, LDH, and uric acid was significant [Table 3].

In this study, maternal complications were analyzed. No complication was observed in controls, whereas 16 out 60 women among cases developed complications. In these women, mean sEng level was almost two times higher (16.27 ± 1.41) as compared to those women who had no other complications (8.49 ± 5.62). The significant intergroup difference was observed between two groups in level of sEng (F = 30.061) ($P < 0.001$). Among women who suffered from maternal complications, two had postpartum hemorrhage, eight had abruption, two had a cerebrovascular accident, and four expired due to eclamptic encephalopathy. All maternal deaths were reported in eclampsia group. Mean serum endoglin level was significantly higher (17.84 ± 0.22) in mothers who died of complications as compared to other women who survived the disease

Table 2: Comparison of serum sEng levels between the groups

Variable	Student's *t*-test	*P*
Group I versus IIa	38.052	<0.001
Group I versus IIb	59.061	<0.001
Group I versus III	34.579	<0.001
Group IIa versus IIb	14.762	<0.001
Group IIa versus III	8.919	<0.001
Group IIb versus III	0.024	0.981

Group I: Control group, Group IIa: Nonsevere preeclampsia, Group IIb: Severe preeclampsia, Group III: Eclampsia, sEng: Soluble endoglin

Table 3: Correlation of serum sEng with biochemical parameters

Variable	Correlation coefficient
Serum uric acid (mg/dL)	
Pearson correlation	*r*=0.722 (strong)
Significant (two-tailed)	<0.001
n	90
Serum LDH (mg/dL)	
Pearson correlation	*r*=0.791 (strong)
Significant (two-tailed)	<0.001
n	90

Two-tailed significance (0.000) this indicate that correlation of sEng was positive, as well as significant. sEng: Soluble endoglin, LDH: Lactate dehydrogenase

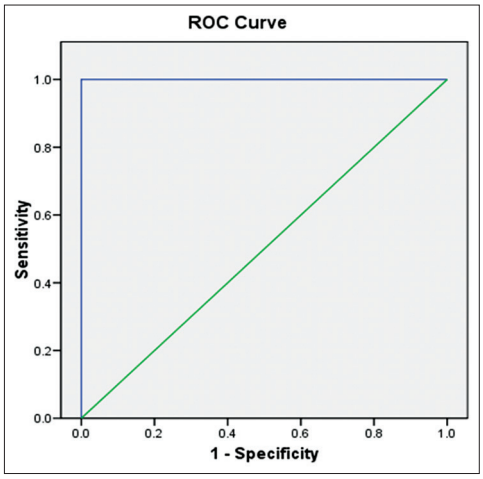

Figure 2: Diagnostic accuracy of serum soluble endoglin (the area under curve 1, at cut-off value >6.26 ng/mL soluble endoglin was 100% sensitive and 100% specific at 95% confidence interval)

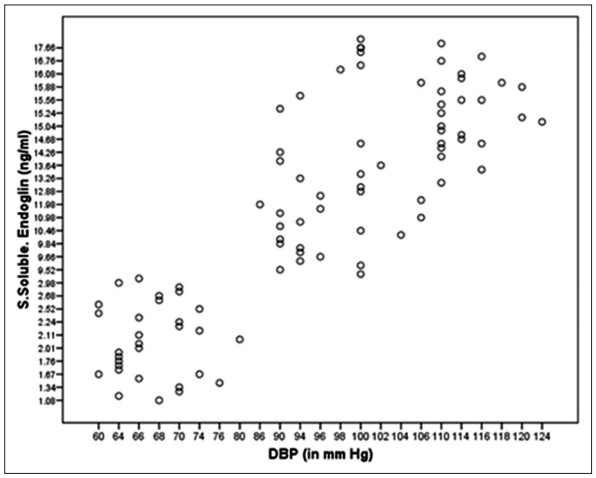

Figure 3: Correlation of serum soluble endoglin with systolic and diastolic blood pressure (systolic blood pressure Pearson's correlation [$r = 0.928$], diastolic blood pressure [$r = 0.916$], $P < 0.001$)

(9.50 ± 5.80) and also the intergroup difference was statistically significant (F = 8.177) (P = 0.005) [Table 4]. This suggests that serum endoglin has prognostic value as its increasing values are associated with more incidences of maternal mortality and morbidity.

DISCUSSION

Various authors have described the role of several biochemical parameters for diagnosis of preeclampsia and results are not encouraging, yet to date no marker has been proved highly efficacious for the disease. So this study was conducted to assess the diagnostic value of sEng level as a biochemical marker of preeclampsia and also to assess its correlation with disease severity, thus evaluating the prognostic value. This study relied on ELISA estimation of only one antiangiogenic factor, sEng as a representative of the diagnostic, as well as a prognostic biochemical marker of preeclampsia. 90 women including 60 cases of preeclampsia, and eclampsia and 30 healthy pregnant women as controls were recruited. In our study, the age wise distribution of subjects in cases was almost similar to controls. The mean age of patients in the cases were ranged from 25.53 ± 4.26 years to 27.47 ± 5.34 years and in controls was 25.37 ± 2.85 years. Our observations were almost comparable to the study conducted by Duhan *et al*.[12] In our study, majority of cases (38/60) belonged to low socioeconomic status. No subject in controls belonged to low socioeconomic status (P < 0.001). This may be suggestive of the fact that due to financial constraints and illiteracy, the cases were deprived of antenatal care and thus the disease was missed at an early stage, thus leading to the onset of severe preeclampsia and eclampsia. With respect to the distribution of cases among different socioeconomic classes, results were similar to our previous study. In our study,[13] more than 50% women were primigravida, but Levine *et al*.[14] reported 80.8% women of preeclampsia were primigravida. Thus, we can support that young age and primigravida are proven risk factors for preeclampsia.

In this study, mean sEng levels was almost seven times higher in severe preeclampsia as compared to controls; however, in the study done by El-Said *et al*.,[15] the mean sEng values were more than 3 times higher in cases as compared to controls. Though the difference between the mean sEng level between cases and controls in both the studies were significant, in our study, we would like to highlight that this difference was highly significant (P < 0.001). This indicates the ability of sEng levels to differentiate between normal and eclamptic pregnancies; supportive of its efficacy as a marker for detection of preeclampsia. Among the cases, there was a highly statistically significant difference in sEng levels in women with severe preeclampsia as compared with those of nonsevere preeclampsia (14.94 ± 0.89 ng/mL vs. 10.21 ± 0.86 ng/mL, respectively). El-Said *et al*.[15] in their study also found a highly statistically significant increase in sEng in the patients with severe preeclampsia compared with those with mild preeclampsia (17.87 ± 2.11 ng/mL vs. 12.03 ± 1.7 ng/mL respectively).

The placenta is suggested to be central to the pathogenesis of preeclampsia. Angiogenic factors like sFlt-1, VEGFR-1 are thought to be important in the regulation of normal placental vascular development[9] and antiangiogenic factor like sFlt-1 and sEng have shown to decrease the trophoblastic migration and invasiveness.[16,17]

In this study, receiver operating curve analysis was used to assess the diagnostic accuracy of sEng. It was observed that at cut-off value of 6.26 ng/mL, it was 100% sensitive and 100% specific at 95% CI for diagnosis of preeclampsia. Findings of our study are in agreement with Gaber *et al*.[18] They showed that ROC curve analyses of serum sEng demonstrated the ability of this marker to differentiate preeclampsia from normal pregnancies. It showed an AUC of 0.962 and at a cut-off value of 7 ng/mL, the sensitivity was 94.4%, and specificity was 87.5%.

Salahuddin *et al*. showed in their study that sEng had sensitivity and specificity of 90% and 95% for differentiating preeclampsia from normal pregnancy.[19]

In our study, the difference in mean SBP and DBP among cases and controls was significant (P < 0.001). The highest value of SBP and DBP was observed in severe preeclampsia group SBP (174.40 ± 12.22) and DBP (112.13 ± 6.9 mmHg). Correlation of SBP and DBP with sEng levels was strong (r = 0.98 for SBP and r = 0.916 for DBP). Elhawary *et al*.[20] also revealed a positive correlation of sEng levels with SBP and DBP. This positive correlation can be explained by the fact that serum endoglin acts by antagonizing, TGF-β1,

Table 4: Maternal outcome

Variable	Total *n* (%)	sEng levels (mean±SD)	Statistical significance
Maternal complication			
No	74 (82.22)	8.49±5.62	*F*=30.061; *P*<0.001
Yes	16 (17.78)	16.27±1.41	
Maternal mortality			
No	86 (95.6)	9.50±5.80	*F*=8.177; *P*=0.005
Yes	4 (4.4)	17.84±0.22	

'*F*': Fisher ANOVA provided '*F*' ratio where a higher '*F*' value depicted a higher intergroup difference. sEng: Soluble endoglin, SD: Standard deviation

an angiogenic growth factor, which is important in mediating nitric oxide-dependent vasodilatation and this is responsible for hypertension.[21]

It is a well-known fact that serum LDH and serum uric acid level are established biochemical marker to assess the severity of preeclampsia. So we, in our study, correlated the values of sEng levels with the value of serum LDH and serum uric acid level. We found a positive correlation between means Eng levels and serum LDH (r = 0.791), similar observation were found when mean serum uric acid was correlated with sEng (r = 0.722). There are yet no studies which have demonstrated the correlation of sEng with LDH or uric acid. This positive correlation with increasing severity of disease and sEng can also predict future prognosis in preeclampsia and eclampsia.

The maternal outcome was analyzed among all the subjects, and it was found that no complication occurred in controls, whereas 16 women among cases had a maternal complication. Eight of cases had abruption, two had postpartum hemorrhage, one had a cerebrovascular accident, and four had expired due to eclamptic encephalopathy. Mean sEng levels were also significantly higher (17.84 ± 0.22) in mothers, i.e., almost twice who expired as compared to other cases (9.50 ± 5.80) who survived the disease. This implies that higher sEng levels are associated with higher maternal morbidity and mortality, thus indicating its prognostic value for the disease, similar findings were reported by Rana *et al*.[22] who demonstrated the levels of sEng were higher in women experienced adverse maternal outcome such as abruption and disseminated intravascular coagulation. Hence, sEng provide prognostic information beyond that supplied by demographic characteristic and clinical presentation. Incorporation of sEng in the evaluation of these patients may allow early identification of patients at risk for the adverse maternal outcome.

CONCLUSION

sEng levels can be used as an emerging biochemical marker for the detection of preeclampsia. However larger studies with large sample size need to be done to determine whether the use of this marker will effectively identify preeclampsia women, thus facilitating the appropriate and timely management of this disease. Our observations also suggest that sEng levels were increased with the severity of disease, in other words, sEng can be used as a prognostic marker in preeclampsia.

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Conflicts of interest

There are no conflicts of interest.

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