Original Article

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Evaluation of Serum Soluble Endoglin Levels in Pre-eclampsia: A Case-Control Study

Obstetrics and Gynaecology Section

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ABSTRACT

Introduction: Soluble Endoglin (sEng) has an antiangiogenic effect, by inhibiting of Transforming Growth Factor (TGF)-β1 bond at endoglin receptors and inhibiting vasodilatation. sEng levels increase in Pre-eclampsia (PE) due to hypoxic placenta and there have been possible role of it in the pathogenesis of PE and its therapeutic implications.

Aim: To compare serum sEng levels in pre-eclamptic patients (cases) versus control.

Materials and Methods: This case-control study was carried out November 2019 to October 2021, in the Department of Obstetrics and Gynaecology, University College of Medical Sciences, Delhi. On 40 cases with a singleton pregnancy with diagnosis of PE enrolled as cases and 40 normal healthy pregnant women matched for age and gestational age as controls. sEng was estimated using commercially available Enzyme- Linked Immunosorbent Assay (ELISA) kit. Last uterine (Ut) and Umbilical Artery (UA) doppler findings were noted and sEng levels were compared with doppler studies. The analysis was done using student t-test and Chi-square test.

Results: A total of 80 participants were included in the study, 40 in case group (mean age 26.53±4.93 years) and 40 in control group (mean age: 25.35±3.10 years). A total of 21 PE cases were Non Severe PE (NSPE) (52.5%) and 19 were Severe PE (SPE) (47.5%). Early-onset PE was observed in n=11 (28%) and the remaining n=29 (72%) had late-onset PE. sEng was significantly higher in pre-eclamptic women 55.08±21.42 ng/mL as compared to controls 44.15±12.02 ng/mL (p=0.006). Higher levels of sEng were seen in SPE 59.20±28.44 ng/mL vs NSPE 51.36±11.66 ng/mL (p=0.066). sEng levels between early onset PE (50.93±5.89 ng/mL) and late onset PE (56.66±24.84 ng/mL) (p=0.832). sEng levels were higher in cases with abnormal Resistance Index (RI) of Ut artery 54.23±6.68 ng/mL than in normal RI of Ut artery 54.23±6.68 ng/mL, though not significant. Abnormal Ut artery RI doppler was seen more in early-onset (n=2, 33%) than in late onset PE (n=1, 7%).

Conclusion: The PE cases had significantly higher levels of sEng compared to controls. Thus, it can be concluded that, there is a definitive role of sEng in pathogenesis of PE due to its antiangiogenic action.

Keywords: Doppler, Early-onset pre-eclampsia, Pulsatility index, Resistance index, Serum soluble endoglin

INTRODUCTION

Despite the uncertain aetiology of PE, it has been seen that angiogenesis defect in the early stages of pregnancy, results in incomplete remodelling of uterine spiral arterioles, abnormal placental vascular development, and endothelial dysfunction as the main cause of PE [1-3]. sEng has an antiangiogenic effect, thereby interfering with the Tumour Growth Factor (TGF)-β1 bond at endoglin receptors on the cell surface, it will inhibit endothelial Nitric Oxide Synthase (eNOS) activation and thereby inhibit vasodilation. It may also cause maternal vascular endothelial dysfunction, and induce endotheliosis [4]. sEng, therefore, is known as an endothelial dysfunction marker [4]. Thus, the role of sEng with other antiangiogenic factors remains a topic of interest. sEng has therapeutic implications, as there has been treatment available that targets and decreases sEng [5-9]. There is a paucity of literature on sEng levels in PE in the Indian population [10]. Hence, the present study was conducted with the aim to evaluate serum sEng levels in PE cases and compare them with control. Comparison of its levels between non severe and severe pre-eclampsia, early-onset and late-onset PE cases were also done. Its levels were also compared with normal and abnormal RI of uterine artery and Pulsatility Index (PI) of umbilical artery doppler velocimetry.

MATERIALS AND METHODS

This was a case-control study, conducted between November 2019 to October 2021 in Delhi, in the Department of Obstetrics and Gynaecology in collaboration with the Department of Biochemistry, University College of Medical sciences and Guru Teg Bahadur Hospital, Delhi. Ethical clearance was obtained from Institutional Ethical Committee for human research (IEC-HR/2019/41/80).

Sample size calculation: In a study conducted by Nabiel Y and Mosbah A [11], the sEng in PE and control were 25.76±3.9 and 14.98±2.39 pg/mL, respectively [11]. In order to detect this difference at a error=5% and power of study=80%, a sample size of 15 cases was required in each group. As per sample size calculation, n=40 cases and n=40 controls were enrolled in the study, of which 40 were women with singleton pregnancy with diagnosis of PE, for termination of pregnancy (dates confirmed by first trimester scan/ sure of dates) meeting the inclusion and exclusion criteria were enrolled as cases and all normal healthy pregnant women matched for age and gestational age were taken as controls.

Inclusion criteria: Those patients diagnosed with PE according to the definition of the ACOG task force on hypertension in pregnancy [12] presenting at the chosen study centre during the study time period were included in the study.

According to task force, [12]:

1) PE is defined as the presence of Systolic Blood Pressure (SBP) greater than or equal to 140 mmHg or a Diastolic Blood Pressure (DBP) greater than or equal to 90 mmHg or higher, after 20 weeks of gestation on two occasions, at least four hours apart in a previously normotensive patient or an SBP greater than or equal to 160 mmHg or a DBP greater than or equal to 110 mmHg or higher.
2) In addition to blood pressure criteria, proteinuria of greater than or equal to 0.3 grams in a 24-hour urine specimen, a protein (mg/dL)/creatinine (mg/dL) ratio of 0.3 or higher or a

urine dipstick protein of 2+ (if a quantitative measurement is unavailable) is required to diagnose PE.

3) In absence of proteinuria, new onset hypertension with thrombocytopenia (Platelet count <1,00,000/μL), renal insufficiency (serum creatinine concentration >1.1 mg/dL or doubling of serum concentration in absence of other renal disease), impaired liver function (elevated blood concentration of liver transaminase to twice the normal concentration), presence of pulmonary oedema or presence of cerebral or visual symptoms are the criteria required for diagnosis.

Exclusion criteria: For case group participants, pregnancy with diabetes mellitus, chronic hypertension, chronic renal failure, premature rupture of the membranes, polyhydramnios, collagen vascular disease, foetal anomalies, asthma, acute respiratory tract infection, smoking were excluded. All normal normotensive women with normal pregnancy age (±2years) and gestational age matched were included as control subjects.

Study Procedure

All subjects were classified into non severe and Severe PE (SPE) on the basis of the following (detailed in [Table/Fig-1]) [13].

Abnormality	Non severe	Severe*
Diastolic BP	<110 mmHg	≥110 mmHg
Systolic BP	<160 mmHg	≥160 mmHg
Headache	Absent	Present
Visual disturbances**	Absent	Present
Upper abdominal pain***	Absent	Present
Oliguria (<500 mL/24 hr)	Absent	Present
Serum creatinine****	Normal	Elevated
Thrombocytopenia (<100,000/μL)	Absent	Present
Serum transaminase elevation	Minimal	Marked (twice normal concentration)
Pulmonary oedema	Absent	Present

[Table/Fig-1]: Classification of Pre-eclampsia (PE) [13].
*SPE may be PE with proteinuria or absence of proteinuria; **scotoma, blurred vision, or diplopia; ***severe persistent right upper quadrant pain or epigastric pain unresponsive to medication; ****creatinine greater than 1.1 mg/dL or a doubling of serum concentration in absence of other renal diseases; BP: Blood pressure

Early onset PE was defined as the onset of hypertension before 34 weeks and late onset PE as after 34 weeks [7]. Blood samples were taken at the time of delivery or induction of labour. A detailed history, general physical examination, and cardiovascular, respiratory and obstetrics examination of all the subjects were performed. All subject's last ultrasound findings were noted and doppler velocimetry was done. Uterine and umbilical artery doppler velocimetry finding was noted and classified as normal or abnormal based on the following parameter

- Umbilical artery doppler velocimetry was defined as abnormal if either the PI was above the 95th percentile for gestational age using or in the presence of abnormal waveforms (absent or reversed end-diastolic velocities).
- Uterine artery doppler velocimetry was defined as abnormal if either the mean RI was above the 95th percentile for gestational age or in the presence of a bilateral early diastolic notch [14].

Determination of serum sEng levels: The serum levels of sEng in women with PE and normotensive pregnant women were measured using sEng Enzyme Linked Immuno-sorbent Assay (ELISA) kit following manufacturer's instructions. The kit was based on the principle of sandwich ELISA:

- Standard curve was constructed by plotting the absorbance obtained from each standard against its concentration with absorbance value on the vertical (Y) axis and concentration on the horizontal (X) axis;
- The corresponding concentration values from the absorbance value of the samples were calculated using a linear curve;
- Serum sEng was thus measured in ng/mL.

STATISTICAL ANALYSIS

Shapiro Wilk test has been used to check normality. Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean±SD and median. Statistical analysis was done as quantitative variables were compared using an independent t-test. Qualitative variables were compared using the Chi-square test. The Receiver Operating Characteristic (ROC) curve was used to find cut-off points of sEng levels for predicting cases and SPE in cases. A p-value of <0.05 was considered statistically significant. The analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

RESULTS

The women in the study group were homogenously distributed in both groups with reference to age, socio-economic status (based on modified kuppuswamy scale) [15], and religion. The socio-economic status of Class III (lower-middle) was seen in majority of cases (58%) and controls (50%) [Table/Fig-2].

Parameters	Cases (n=40)	Control (n=40)	p-value
Age (in years)*	26.53±4.93	25.35±3.10	0.206
≤25 years$	18 (45%)	21 (53%)	0.246
26-30 years$	16 (40%)	18 (45%)	
31-35 years$	4 (10%)	1 (2%)	
>35 years$	2 (5%)	0	
Gestational age at delivery*	37.1±2.0	37.78±2.172	>0.05
Place of residence$			
Rural	7 (18%)	13 (33%)	0.121
Urban	33 (82%)	27 (67%)	
Socio-economic status$			
Class I (upper)	1 (3%)	0	0.393
Class II (upper-middle)	6 (15%)	4 (10%)	
Class III (lower-middle)	23 (58%)	20 (50%)	
Class IV (upper-lower)	10 (25%)	16 (40%)	
Class V (lower)	0	0	
Religion$			
Hindu	21 (53%)	26 (65%)	0.256
Muslim	19 (47%)	14 (35%)	
Occupation$			
Housewife	35 (88%)	35 (88%)	1.000
Employed	5 (12%)	5 (12%)	

[Table/Fig-2]: Comparison of socio-demographic characteristics of the study groups.
Using *student t-test and $Chi-square test p-value ≤0.05 has been considered as significant

Mean Body Mass Index (BMI) was significantly higher in cases 22.29±2.76 kg/m^2 than in control 21.2±2.06 kg/m^2 (p<0.05). Out of 40 cases of PE, n=21 cases were NSPE and n=19 were SPE. Out of 19 SPE, there were n=6 cases of Haemolysis, Elevated Liver enzymes, and Low Platelets (HELLP) (32% of SPE) and out of which n=2 cases were partial HELLP with thrombocytopenia alone and the rest had complete HELLP (2 or more features). Out of 11 cases of early-onset PE, n=6 (55%) developed SPE vs n=5 (45%) who developed NSPE. While in late onset PE out of 29 cases, n=13 (45%) had progressed to SPE.

The most common maternal complication in the present study was pulmonary oedema n=9 (47%) [Table/Fig-3]. Out of 10 Foetal Growth Retardation (FGR) cases, FGR was higher in severe cases (n=7, 37%) vs NSPE (n=3, 14%). Also, deranged doppler with FGR were more in severe cases (n=4, 21%) than NSPE cases (n=3, 14%).

Majority (n=28, 70%) of women in pre-eclamptic group underwent induction of labour (iatrogenic) as compared to the controls (n=33, 83%) who went into labour spontaneously. Caesarean section rates were higher in pre-eclamptic cases (n=14, 35%) compared to controls (n=2, 5%) (p-value=0.003). Preterm delivery rates were higher in SPE (n=8, 42%) cases than NSPE cases (n=7, 33%). The mean neonatal birth weight among the pre-eclamptic cases 2.19±0.46 kg was significantly lower than control 2.65±0.44 kg (p<0.001). Thus, rate of NICU admission was higher in SPE (47%, n=9) than NSPE (10%, n=2). Out of the nine NICU admissions, two neonatal mortalities occurred due to prematurity and sepsis belonged to SPE group. There was no maternal mortality.

Characteristics	Non Severe Pre-eclampsia (NSPE) N=21 (52.5%)	Severe Pre-eclampsia (SPE) N=19 (47.5%)	p-value
Onset of pre-eclampsia (PE)			
Early (<34 weeks) (n=11)	5 (24%)	6 (32%)	0.583
Late (>34 weeks) (n=29)	16 (76%)	13 (68%)	
Symptoms of impending eclampsia			
Headache	0	11 (58%)	-
Blurring of vision	0	6 (32%)	
Epigastric pain	0	0	
Oliguria	0	1 (5%)	
Maternal complications			
HELLP syndrome	0	6 (32%)	-
Deranged lab investigations	0	2 (11%)	
Low platelets (thrombocytopenia)			
Low platelet+increased transaminases (partial HELLP)	0	2 (11%)	
Low platelet+increased transaminases+haemolysis (HELLP)	0	2 (11%)	
Deranged KFT	0	1 (5%)	
Complications			
Renal	0	1 (5%)	-
Liver (Jaundice)	0	2 (11%)	
Deranged coagulation	0	1 (5%)	
Cardiovascular	0	0	
Respiratory (pulmonary oedema)	0	9 (47%)	
Neonatal complication			
Foetal Growth Retardation (FGR) with normal doppler	0	3 (15%)	0.049
FGR with deranged doppler	3 (14%)	4 (21%)	
Neonatal outcomes			
Preterm	7 (33%)	8 (42%)	0.109
Term	14 (67%)	11 (58%)	
NICU admission	2 (10%)	9 (47%)	
Neonatal mortality	0	2 (11%)	

[Table/Fig-3]: Comparison of complications between Non Severe PE (NSPE) and Severe PE (SPE).

Mean value of sEng was significantly higher in pre-eclamptic women 55.08±21.42 ng/mL as compared to controls 44.15±12.02 ng/mL in Indian population (p=0.006) as shown in [Table/Fig-4].

Higher levels of sEng were seen in SPE (59.20±28.44 ng/mL) compared to NSPE (51.36±11.66 ng/mL), though not significant (p-0.066) [Table/Fig-5].

Parameter	Cases (mean±SD)	Control (mean±SD)	p-value
Serum soluble endoglin (sEng) level (ng/mL)	55.08±21.42	44.15±12.02	**0.006**

[Table/Fig-4]: Comparison of serum soluble Endoglin (sEng) levels between cases and controls.
Using student t-test *p-value≤0.05 has been considered as significant

Parameter	Non Severe Pre-eclampsia (NSPE) cases (n=21) Mean±SD	Severe Pre-eclampsia (SPE) cases (n=19) Mean±SD	p-value
sEng (ng/mL)	51.36±11.66	59.20±28.44	0.066

[Table/Fig-5]: Comparison of serum Soluble Endoglin (sEng) level between severe and Non Severe Pre-eclampsia (NSPE).
Using student t-test *p-value ≤0.05 has been considered as significant

No significant difference (p=0.832) was seen in the mean value of sEng levels between early onset PE (50.93±5.89) and late onset PE (56.66±24.84) [Table/Fig-6]. sEng levels (54.23±6.68 ng/mL) were higher in cases of abnormal RI of uterine artery than in normal RI of uterine artery (52.01±22.16 ng/mL) though not significant (p=0.865). When mean value of sEng was compared in pre-eclamptic with normal PI of umbilical artery (52.62±22.32 ng/mL) and abnormal PI of umbilical artery (48.25±9.47 ng/mL) no significant difference was found [Table/Fig-7]. Abnormal uterine artery RI doppler was seen more in early-onset (n=2, 33%) than in late onset PE (n=1, 7%). However, abnormal umbilical artery PI doppler was seen more in late-onset PE (n=3, 21%) than in early-onset PE (n=1, 17%).

Parameter	Early-onset PE cases (n=11) Mean±SD	Late-onset PE cases (n=29) Mean±SD	p-value
Serum soluble endoglin levels (ng/mL)	50.93±5.89	56.66±24.84	0.832

[Table/Fig-6]: Comparison of serum Soluble Endoglin (sEng) level between early and late-onset Pre-eclampsia (PE).
Using student t-test *p-value≤0.05 has been considered as significant

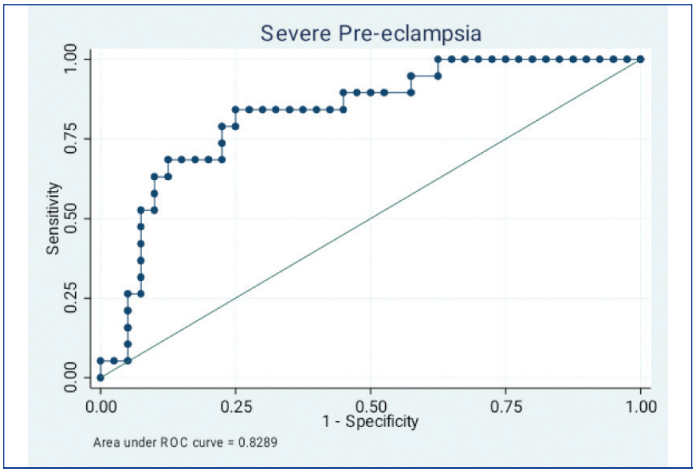
Parameters	RI of uterine artery (n=20)		p-value
	Normal cases (n=17) Mean±SD	Abnormal cases (n=3) Mean±SD	0.865
sENG (ng/mL)	52.01±22.16	54.23±6.68	
	PI of umbilical artery (n=20)		p-value
	Normal cases (n=16) Mean±SD	Abnormal cases (n=4) Mean±SD	0.703
sENG (ng/mL)	52.62±22.32	48.25±9.47	

[Table/Fig-7]: Comparison of serum Soluble Endoglin (sEng) levels with uterine artery RI and umbilical artery PI in pre-eclamptic cases.
Using student t-test *p-value ≤0.05 has been considered as significant
Due to Coronavirus Disease-2019 (COVID-19) pandemic we had limited resources, therefore we were only able to do doppler in 20 cases and 20 controls. Here n=20 is of cases. No doppler changes were noted in n=20 controls

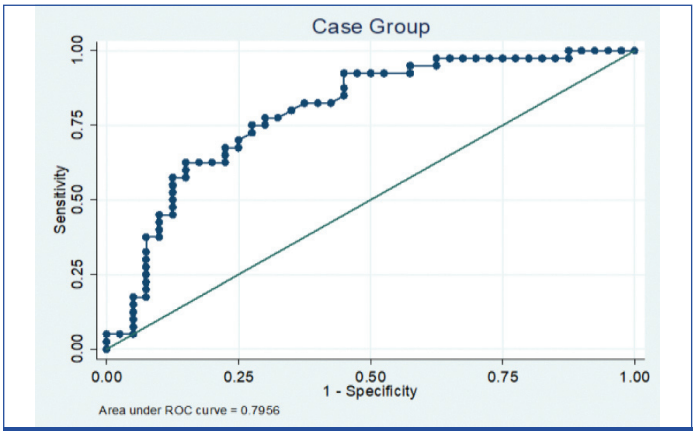
The authors plotted two curves for predicting PE cases and SPE cases. [Table/Fig-8,9] shows sEng levels for predicting SPE cases had Area Under Curve (AUC) (0.829) whereas [Table/Fig-10] shows sEng levels for predicting PE cases had AUC (0.795). On plotting Receiver Operating Characteristic (ROC) curve, the cut-off for predicting PE cases was 47.94 ng/mL with sensitivity of 67.50%, specificity of 75%, positive predictive value 72.97% and negative predictive value 69.77% and AUC of 0.795. The cut-off for predicting SPE cases were 46.5 ng/mL with sensitivity 84.21% n specificity 67.50%, positive predictive value 55.17% and negative predictive value 90%.

Parameters	For predicting PE cases	For predicting Severe Pre-eclampsia (SPE) cases
Area under the ROC curve (AUC)	0.795	0.829
Sensitivity	67.50%	84.21%
Specificity	75.00%	67.50%
Positive predicted value	72.97%	55.17%
Negative predicted value	69.77%	90.00%
Accuracy	71.25%	72.88%
Best cut-off (ng/mL)	47.94	46.5

[Table/Fig-8]: Receiving Operating Characteristic (ROC) curve of Soluble Endoglin (sEng) levels for predicting cases and Severe PE (SPE) in cases.
Soluble Endoglin (sEng) levels (ng/mL)



[Table/Fig-9]: ROC curve of serum Soluble Endoglin (sEng) levels for predicting severe pre-eclampsia (PE) in cases.



[Table/Fig-10]: ROC curve of serum Soluble Endoglin (sEng) levels for predicting pre-eclampsia (PE) in cases.

DISCUSSION

The defective vascular remodelling and a hypoperfused placenta, resulting from the shallow cytotrophoblast migration toward the uterine spiral arterioles. The placenta becomes ischaemic which leads to the release of angiogenic factors that are associated with maternal vascular endothelial dysfunction. sEng is one such antiangiogenic factor [17]. sEng is a cell surface co-receptor that binds to and decreases levels of TGF-b, which induces migration and proliferation of endothelial cells [18]. sEng has an antiangiogenic effect, which is by interfering the TGF-1 bond at Eng receptors on the cell surface, it will inhibit endothelial Nitric Oxide Synthase (eNOS) activation and result in no vasodilation. It may also cause maternal vascular endothelial dysfunction [19,20]. These aspects mediate downstream effects, that create endothelial dysfunction, a vasoconstrictive state, oxidative stress, and microemboli, which contribute to the involvement of multiple organ systems, and thus, the clinical features of PE [18].

Rana S et al., studied plasma concentration of sEng and found it significantly higher in women with PE (30.2 ng/mL) and gestational hypertension (6.2 ng/mL) compared to women with no hypertensive disorder (4.8 ng/mL) [21]. They used a cut-off of 12 ng/mL for sEng. The authors also observed that sEng were significantly higher in pre-eclamptic group 55.08±21.42 ng/mL compared to controls 44.15±12.02 ng/mL (p=0.006). The cut-off for predicting pre-eclamptic cases in the present study is 47.94 ng/mL. Nikuei P et al., studied that the mean serum level of sEng in women with mild PE was 24.08±3.05 ng/mL and SPE was 26.34±3.37 ng/mL as compared to controls 13.58±5.80 ng/mL [22]. They also found there was a significant increase in early onset (26.10±2.68 ng/mL) compared to late onset PE (24.62±3.47 ng/mL). However, in our group the mean value of sEng in late onset PE (56.66±24.84 ng/mL) was higher than early onset PE (50.93±5.89 ng/mL) as there were fewer cases in early onset PE compared to late onset PE our data is limited. Nabiel Y and Mosbah A studied maternal sEng level and cell free foetal Deoxyribonucleic Acid (DNA) in PE [11]. Similar results were found, the means in pre-eclamptic cases is significantly higher than in the control group. Also, the authors in the present study observed that the mean levels of sEng were higher in SPE compared to NSPE though not significant. Hence, the authors can imply that there is correlation between increasing levels of sEng and severity of PE.

Gaber K et al., studied sEng levels in gestational hypertensives, pre-eclamptic and controls during 14-18 weeks of gestation and followed till delivery [23]. They found that the level of sEng was significantly higher in PE and gestational hypertension in comparison to control group. However, the results of these studies cannot be compared to the present study as our enrollment of cases was after onset of PE. A detailed review of literature shows increased level of sEng in PE, summarised in [Table/Fig-11] [11,14,21,22,24].

sEng levels and its correlation with Doppler studies: literature has shown abnormal umbilical and uterine doppler having higher sEng levels compared to those with normal doppler flow [14,24]. The authors also studied the correlation of sEng with normal and abnormal RI of uterine artery and PI of umbilical artery detailed in [Table/Fig-3]. The present study was in coherence with study of Chaiworapongsa T et al., and Tobinaga CM et al., [14,24]. Chaiworapongsa T et al., observed that abnormal UT and UA doppler velocimetry had highest sEng levels compared to other groups [14]. In the present study, due to limited resources, the authors were able to conduct doppler in only 20 cases and controls. However, in the present study, no significant difference was found in relation between sEng and abnormal PI of umbilical artery (p=0.703). Tobinaga CM et al., found patients with early-onset PE had higher mean uterine artery doppler than late-onset [24]. Similarly, in the present study, the authors found that abnormal uterine artery doppler was seen more in early-onset (33%) than in late onset PE (7%). However, abnormal umbilical artery doppler was

Study	Year and place	Case and control	Recruitment age	sEng levels	SPE/NSPE	Other findings	Conclusion
Rana S et al., [21]	2012 Boston	56 vs 114	<34 weeks	6.2 ng/mL vs 30.2 ng/mL vs 4.8 ng/mL	GHTN vs PE vs controls	Cut-off- 12 ng/mL Sn- 80.4% Sp-88.6% PPV- 77.6% NPV- 90.2%	sEng levels were higher in PE and GHTN vs control. Comparison was not between early vs late-onset PE and with doppler studies
Nikuei P et al., [22]	2017 Iran	41 vs 20	After onset of PE	24.08±3.05 ng/mL 26.34±37 ng/mL 13.58±5.80 ng/mL 26.10±2.68 ng/mL 24.62±3.47 ng/mL	Mild PE/SPE/ controls Early-onset/ late- onset PE	Cut-off-≥20.4 Sn-92.1% Sp-90% PPV-94.6% NPV-85.7%	Increased sEng in both mild and severe groups than control. Also increase sEng in early-onset and late-onset vs controls. Correlation with doppler studies was not done.
Nabiel Y and Mosbah A [11]	2019 Egypt	80 vs 80		25.76±3.90 pgm/mL vs 14.98±2.39 pgm/mL 29.71±2.54 pgm/mL vs 24.30±3.34 pgm/mL 23.38±2.65 pgm/mL vs 29.96±1.34 pgm/mL	PE vs Controls Early-onset vs late-onset PE Mild PE vs SPE	Cut-off-19.22 pg m/mL Sn- 97.5% Sp-98.8% NPV-98.7% Accuracy-98.1%	sEng were higher in PE cases than control, higher in early-onset than late-onset PE and higher in severe than mild PE. Correlation with doppler studies not done.

Chaiworapongsa T et al., [14]	2010 Michigan	69 Vs 135	After onset of PE	sEng levels more in PE	Normal vs PE	Doppler findings- Uterine artery RI in PE (n=44 alone, n=11-combined) 0.69±0.16 Umbilical artery PI-1.3±0.9 (n=3 alone, n=11 combined)	Among pre-eclamptic, those with abnormal UT and UA Doppler have highest sEng. While women with PE with normal Doppler in both vessels have lowest sEng.
Tobinaga CM et al., [24]	2014 Brazil	54 vs 54	28-36 weeks gestation	7.9 (3.8) ng/mL vs 46.9 (38.3) ng/mL 63.4 (41.8) ng/mL vs 31.4 (26.1) ng/mL	Control vs PE Early-onset vs late-onset PE	Doppler findings- Uterine artery RI-0.49 (0.07) vs 0.63 (0.11) 0.67 (0.10) vs 0.58 (0.11) Umbilical artery doppler- >95th percentile for GA.	sEng was higher in PE than controls. Higher in early-onset than late-onset PE. This increase is directly correlated with uterine artery resistance. Only 3.7% PE had abnormal umbilical artery doppler.
Present study	2021	40 vs 40	At time of labour/ induction	55.08±21.42 ng/mL vs 44.15±12.02 ng/mL 51.36±11.66 ng/mL vs 59.20±28.44 ng/mL 50.93±5.89 ng/mL vs 56.66±24.84 ng/mL 52.01±22.16 ng/mL vs 54.23±6.68 ng/mL 52.62±22.32 vs 48.25±9.47 Cut-off for predicting cases- 47.94 ng/mL Sn- 67.50% Sp- 75% PPV- 72.97% NPV- 69.77%	Cases vs controls. N SPE vs SPE. Early-onset PE vs Late-onset PE RI of uterine artery Normal vs abnormal cases PI of umbilical artery: Normal vs abnormal	Doppler findings: Uterine artery RI in PE vs controls(n=20) 0.54±0.21 vs 0.46±0.04 Umbilical artery PI in PE vs controls (n=20)-0.97±0.87 vs 0.95±0.09	sEng levels were higher in PE cases compared to controls. The levels were higher in SPE compared to non severe, late- onset PE compared to early-onset PE. sEng levels (54.23±6.68 ng/mL) were higher in cases of abnormal RI of the uterine artery though not significant (p=0.865). But the present study did not match with general consensus in literature for umbilical artery.

[Table/Fig-11]: Soluble Endoglin (sEng) levels in PE and controls in literature [11,14,21,22,24].

seen more in late-onset PE (21%) than in early-onset PE (17%). As doppler studies were done only in limited cases and controls, more number would be needed for further research. The strength of this study was that this was a case-control study model in a previously uninvestigated population from the Indian subcontinent. The study had a prospective study design and all the subjects were matched for age and gestational age. All pre-eclamptic cases i.e., non severe and severe, early- and late-onset PE were included in the present study and compared. The cases group was also compared with control group for sEng levels. The present study focused on a well-defined PE group excluding gestational hypertension and chronic hypertension cases to decrease ambiguity of pregnancy related hypertensive case definition. Present study also compared PE complications with sEng levels. The authors also included RI of uterine artery and PI of umbilical artery in the present study to learn more about the pathogenesis of sEng in PE.

Limitation(s)

Gestational and chronic hypertension cases were not included in the present study. The result of only one hospital cannot be generalised for all settings. Doppler study was done on a limited number of cases and controls due to COVID-19 pandemic resources were limited. Enrollment of cases was done at induction of labour and not from early gestation to help to predict pre-eclampsia.

CONCLUSION(S)

The PE cases had higher levels of sEng compared to controls and SPE had higher levels of sEng compared to NSPE though not significant. Higher levels were associated with severe manifestations. Abnormal RI uterine artery doppler associated with higher levels of sEng, though not significant. Also, abnormal uterine artery doppler was seen more in early-onset than in late-onset PE. Thus, it can be concluded that there is a definitive role of sEng in pathogenesis of PE due to its antiangiogenic action.

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