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Maternal Serum Soluble Endoglin Levels as a biomarker in Preeclampsia: A Case Control Tertiary Care Hospital Based Study

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Preeclampsia (PE) is a multifactorial pregnancy specific disorder with complexity in pathophysiology. Many markers have been evolved but none of them was specific. The aim of the study was to compare the maternal serum soluble endoglin (sEnd) levels in pre-eclamptic & normotensive pregnant women in early and late gestational weeks. A total of 300 subjects were enrolled from the R.L.Jalappa Hospital and Research Centre, Obstetrics & Gynaecology department. In this case-control study design the cases were 150 subjects who were diagnosed as pre-eclamptic women and controls are 150 normotensive pregnant women who are healthy without any complications till delivery. Both in cases and controls the subjects were after 20 weeks of gestation. By taking written informed consent from each participant the 5ml of blood was collected and measured for the estimation of sEnd levels by using commercially available kits. The Area under Receiver Operating Characteristic Curve was calculated by using Statistical Packages for Social sciences Software with values 0.87 with 87% sensitivity and 83% specificity with cut off value = 8 ng/ml. The sEnd levels are significantly increased in preeclamptic women than normotensive pregnant women (P=0.0001).So sEnd can be a diagnostic marker for PE in Kolar population. This is the first south eastern Indian study with 300 sample size.

Keywords: CD105; Hypertensive Pregnancy Disorders; Preeclampsia Antiangiogenic Factors; Pregnancy Diagnostic Marker; Soluble Endoglin.

PE is a multisystemic pregnancy hypertensive syndrome with improper implantation of placenta, and vascular endothelial impairment. The incidence of hypertensive pregnancy disorders in worldwide is 5 to 7% which contribute for the maternal and fetal morbidity and mortality[1]. PE itself contributes 7 to 10% in maternal and fetal morbidity and mortality[2]. During pregnancy, the placenta undergoes angiogenesis and vasculogenesis to accommodate fetal demands. Due to defective angiogenesis mechanism there will be imbalance in secretions of placental angiogenesis during placental development, followed by endothelial vascular disorders, hypertension, proteinuria and

preeclampsia (PE)[1, 3].The pathophysiology of PE was explained as a two stage disease. The early-stage: decrease in cytotrophoblastic invasion of uterine spiral arterioles and leads to utero-placental vascular insufficiency. Late-stage: Due to delicate placenta there will be an imbalance in soluble angiogenic factors leads to systemic endothelial dysfunction[4]. Based on gestational weeks, PE was further classified as early-onset and late onset PE. Early onset PE is which occurs before 34 weeks, due to improper implantation of placenta categorized by placental lesions and diminished in fetal development which leads to fetal and maternal consequences. Whereas late-onset PE occurs on or late 34 weeks but was much related to pre-existing maternal factors like obesity, metabolic syndrome, dyslipidemia but not appreciated with fetal development[5]. In patching together to PE and angiogenesis, in PE there will be an imbalance in proangiogenic (Placental Inhibitor Growth Factor) and antiangiogenic factors (Soluble Fms Like Tyrosine Kinase-1, Soluble Endoglin factors) in the maternal blood distribution. Endoglin is expressed by placental endothelial cells of chorionic villi (syncytiotrophoblasts) at 11 weeks of gestation [6]. Placental Endoglin releases soluble Endoglin into the maternal blood flow. Soluble Endoglin (sEng) is an antiangiogenic, endothelial cell impairment indicator and PE marker with a molecular weight of 180 KD. During gravida status, the vital performance of endoglin in normotensive pregnant women is to control the multiplication, differentiation, incursion of trophoblastic cells to regulate endothelial cell proliferation, and blastocyst implantation. The pathogenesis of PE is associated with placental abnormalities and vascular remodeling. As placental vessels were damaged and by desquamation of membrane-bound sEng isoform transforming growth factor-beta (TGF- â) there will be vasoconstriction. so sEng isoform prevents cell signaling and endothelial function and this results in decreased blood flow and increased levels of sEng[6]. The over-expressed placental endoglin will be relieving sEng into the maternal circulation[7].The released sEng in maternal blood binds with TGF-â (family), by inhibiting the stimulation of endothelial nitric oxide synthase (eNOS) decreases nitric oxide leads to hypoxic conditions. Due to hypoxic environment in the placenta along with increased sEng levels in maternal circulation tempted to effect vascular functioning by increasing in vascular permeability, endothelial dysfunction. The placental hypoxia leads to placental ischemia[6]. Due to imbalance in the pathway leads to lose control over the trophoblastic invasion of cells and leads to discrepancy which will induce hypertension, which is a cardinal feature in PE [2,7]. Due to complexity in PE etiology is imprecise. So many studies have paved a way for different diagnostic markers but none has concluded with specific diagnostic and prognostic markers. So we hypothesized that there will be a relation between increased levels in sEnd to the gestational weeks in maternal serum of normotensive pregnant women and preeclamptic women. In PE or with suspected PE there will be elevated levels of sEnd have been proven by many studies, but with gestational weeks comparison are hardly few studies are there. So this study aim is to compare the maternal serum soluble endoglin (sEnd) levels in pre-eclamptic & normotensive pregnant women in early and late gestational weeks.

MATERIALS AND METHODS

Study center

This study was conducted in the Sri Devaraj Urs Academy of Higher Education and Research in R.L.Jalappa Hospital and Research Centre in the Department of Obstetrics & Gynaecology. After the doctoral committee approval with the number: SDUAHER/ KLR/ CEC/61/2020-2021, the study subjects were collected along with the written informed consent from each subject.

Study details

In this case-control study, 348 pregnant women were involved, out of these 16% withdrawn from the study. The details were 10% of pregnant women were shifted to their home town for delivery (parents' house). About 4% of subjects were not concerned to give sample but shared the history and the remaining 2% developed gestational diabetes at late gestational weeks [8].In this study, 150 pregnant women were diagnosed with PE, based on the American College of Obstetrics and Gynaecologists in the Department of Obstetrics & Gynecology in R. L. Jalappa Hospital & Research Centre [8,9]. The 150 were cases who were diagnosed

as PE and other 150 were controls considered as normotensive pregnant women.

Included in the study

Cases: Pregnant women who were diagnosed with PE e 20th week of gestation, both primigravida and multigravida with early and late gestational weeks of the reproductive age (18-40 years).

Controls: The healthy pregnant women e 20th week of gestation no obstetric and medical complications till delivery, primigravida and multigravida with early and late gestational weeks [8], spontaneous vaginal delivery.

Elimination Measures

Cases: Pregnant women with gestational hypertension, chronic hypertension, gestational diabetes, previous history of more than 2 abortions, previous pregnancy with an anomalous fetus, and thrombophilia like disorders [8].

METHODOLOGY

Explained in figure1 [8]

Data analysis and Statistical Interpretation

The statistical analysis of data was performed by using Statistical Packages for Social Sciences Software SPSS (version 22.0; SPSS Inc, Chicago, IL, USA). Due to non-distribution in variance, the statistical data (mean, median) was analysed by the Mann-Whitney U test (non-parametric test). The sensitivity (true positive) and specificity (false positive) were interpreted as receiver-operating characteristics of area under curves using SPSS (version 22.0; SPSS Inc, Chicago, IL, USA)

RESULTS

The statistical analysis of samples (cases and controls) were calculated by using the Statistical Packages for Social Sciences software SPSS (version 22.0; SPSS Inc, Chicago, IL, USA). Out of 300 subjects, the pregnant women with early gestational weeks were 46 and late gestation was 254 participants and according to gravida status primigravida were 149 and multigravida were 151, the details were given in Table 1. The severe PE was 68% and the remaining were mild PE described in Table 1. Maternal age, gestational

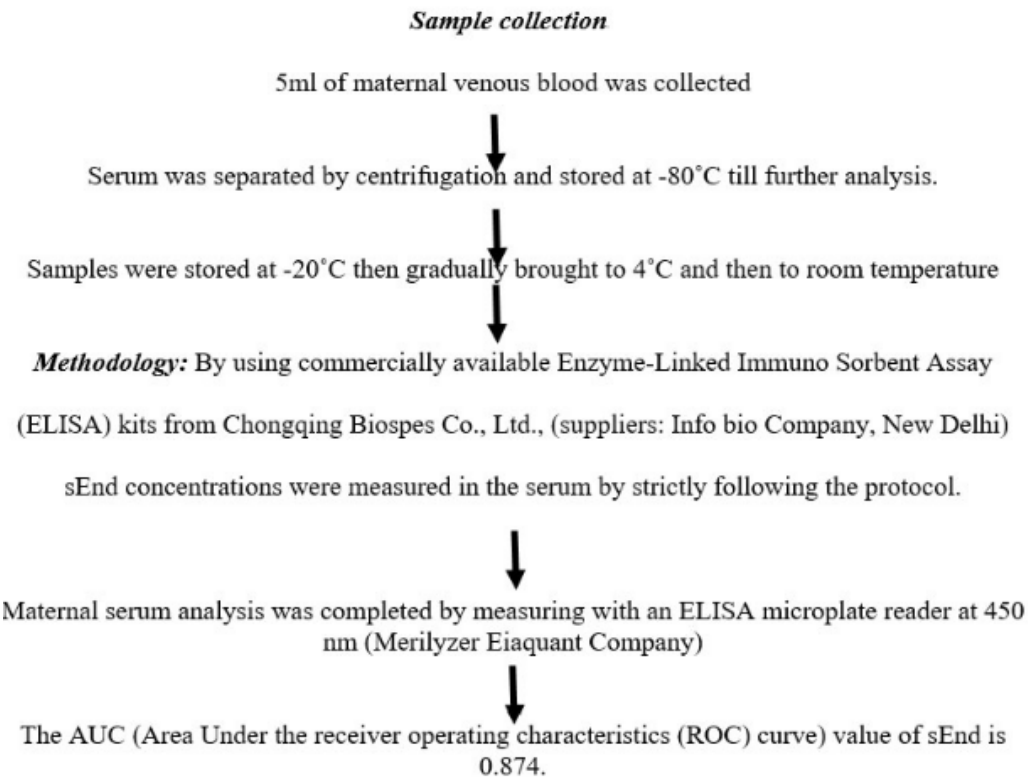

Fig. 1. Sample collection

weeks, systolic, and diastolic blood pressures in cases and controls were analyzed by the Mann-Whitney U test explained in Table 2. Due to non-distribution in data, the statistical significance of the maternal sEng levels in cases and controls were analyzed by the non-parametric Mann-Whitney U test explained in Table 3. By comparing cases and controls the maternal serum sEng levels were significantly higher in PE cases (z value =8.71).The p-value is significant with d"0.0001 especially if we compare with early and late gestational weeks in late gestational weeks the sEng levels were highly significant. The AUC curve value is 0.87 with 89% and 83% sensitivity and specificity were observed with a cut off value of e"8 ng/ml in Table 3 and figure2. If the value of maternal serum sEnd levels were e"8 ng/ml are prone to PE. In 52.6% primigravida were PE patients so this reveals PE is more prone to primigravidae. The median values of maternal age in cases and controls there was no much difference between early and late gestation, but in gestational age, we found a difference in late & early PE. In late PE the gestational weeks are 37 and in subjects with early PE were 30 weeks only and if you compare with controls the late gestation extended to 39 weeks. So this proves that due to PE there were more chances of pre-term delivery which affects fetal growth. If we compare the serum

Table 1. Gravida status and gestational weeks of subjects participated in Case - Control study

Gravida status	Number of Cases (n=1 50)	Number of Controls (n=150)
Primigravida	79 (52.6%)	70 (46.6%)
Multigravida	71 (47.3%)	80 (53.3%)
Early Gestation	36 (24%)	10 (6.6%)
Late Gestation	114 (76%)	140 (93.3%)
Severe PE	102 (68%)	———————-
Mild PE	48 (32%)	———————-

n- Number of subjects, Cases- Preeclamptic pregnant women and Controls – Normotensive pregnant women, PE-Preeclampsia

Table 2. Statistical Outcomes in Early and Late Preeclamptic Women (Cases) vs Early and Late Normotensive Pregnant Women (Controls).

Content	Gestational Weeks	Median± SE	P value
Maternal Age	Early Gestational Weeks in PE cases	25 ± 0.616	0.1336
	Early Gestational Weeks in controls	23 ± 1.13	
	Late Gestational Weeks in PE cases	24 ± 0.40	0.1141
	Late Gestational Weeks in controls	24 ± 0.267	
Soluble Endoglin levels	Early Gestational Weeks in PE cases	31340 ±11180	*0.00001
	Early Gestational Weeks in controls	640 ± 195	
	Late Gestational Weeks in PE cases	21270± 1660	*0.00001
	Late Gestational Weeks in controls	480 ±85	
Systolic Blood Pressure	Early Gestational Weeks in PE cases	160±4.18	*0.00001
	Early Gestational Weeks in controls	115±4.216	
	Late Gestational Weeks in PE cases	110±3.39	*0.00001
	Late Gestational Weeks in controls	120±0.757	
Diastolic Blood Pressure	Early Gestational Weeks in PE cases	110±3.39	*0.00001
	Early Gestational Weeks in controls	70 ± 2.62	
	Late Gestational Weeks in PE cases	100 ± 1.44	*0.00001
	Late Gestational Weeks in controls	70 ± 0.586	
Gestational Age	Early Gestational Weeks in PE cases	30 ±0.384	0.8807
	Early Gestational Weeks in controls	29.5 ±0.87	
	Late Gestational Weeks in PE cases	37 ± 0.180	*0.00001
	Late Gestational Weeks in controls	39 ± 0.128	

*Significant with p value d" 0.0001, SE- Standard Error,
Number of subjects involved in the study were as follows:
Early Gestational Weeks in PE cases n=36; Early Gestational Weeks in controls n=10;
Late Gestational Weeks in PE cases n=114; Late Gestational Weeks in controls n=140

sEng levels in early and late PE, in early gestational weeks of PE the serum sEng levels are high in Table 2.

DISCUSSION

The endoglin function is to maintain vascular tone. Due to PE there will be increased levels of circulating endoglin levels which are associated with vasoconstriction, resulting in decreased blood flow, hints to placental hypoxia leading to placental ischemia which stimulates to release sEnd into the maternal blood flow [6,10,11]. The increased concentration of sEnd leads towards placental ischemia eventually leads to endothelial damage. According to Akbar *et al* in their study mentioned that increased sEnd levels was observed at 12-16 weeks before the onset of PE[6]. According to the Kosinska-Kaczynska *et al* in a review stated that sEnd increased levels were significant at 31 to 35 gestational weeks [12]. According to the study by Gaber *et al* concluded that sEnd can be a predictive marker of PE at 15– 18 gestational weeks. If with a cutoff value of >7 ng/ ml, 94% chances are there to develop PE[13]. In a review piloted by Chen states that the sEnd cut off value ranges from 4.1 to 33 ng/ml [14]. The present study results match with Gaber and Chen studies, the cut off values are similar with the present study population. In a study performed by Ali and his colleague's states that sEnd levels were significant in PE group with mean value 9.1+44.3-17[1]. A study performed in Romania stated that sEnd levels are not so relevant for diagnostic use in PE of Romanian population[15]. A study with 43 PE women was performed in Brazil found that sEnd levels remained constantly high in severe PE. But in the present study was performed by comparing to gestational ages in PE. In early PE the sEnd concentration levels were significant than late PE, but definitely there was an increase in serum sEnd concentrations between normotensive and PE pregnant women. A

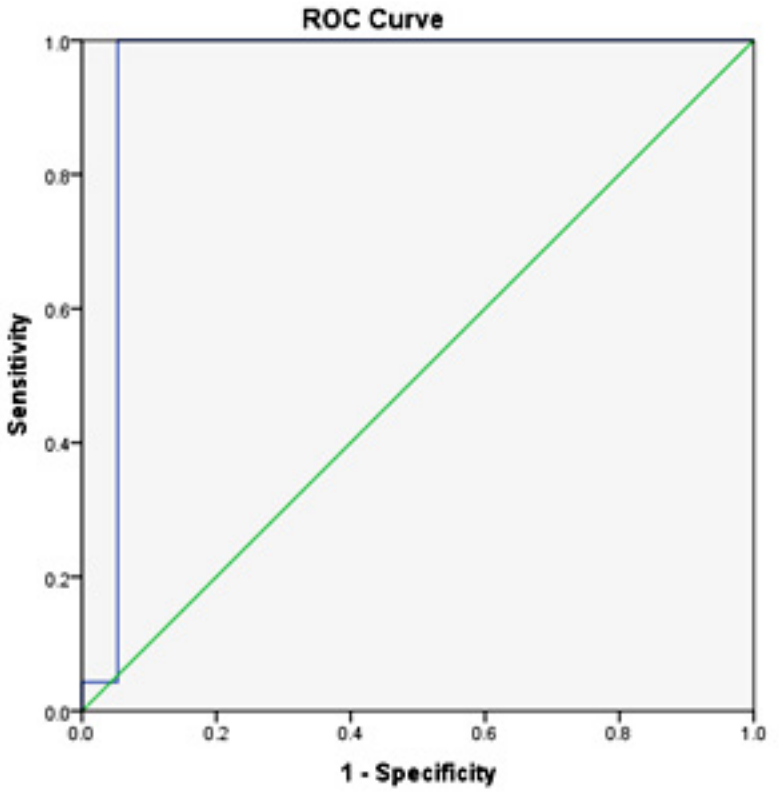

Fig. 2. AUC curve of soluble Endoglin value
The AUC value of soluble Endoglin is 0.87 with 89% sensitivity and 83% specificity with a cut off value of ≥8 ng/ml

Table 3. Angiogenic Marker- Soluble Endoglin Statistical Values

Content	Median ± SE	IQ Range	AUC value	Sensitivity	Specificity	Cut -off value	P-value
In both cases & controls	88.25 ± 5.17	138-37.25=100.75	0.87	89%	83%	pg/ml	U= 4705
PE Z=8.71	29.7 ± 5.66	160.3 -102 = 58.37	NA	NA	NA	N	A
Controls	50 ± 8.03	81.125-20.87= 60.25	NA	NA	NA	NA	*0.0001

*Significant with p value d" 0.0001, IQ Range- Inter Quartile Range, SD-Standard Deviation,
SE-Standard Error, NA- Not Applicable, AUC- Area under the receiver –operating characteristics

study piloted by Hirashima *et al* on 56 PE women, states that in the early onset of PE the sEnd levels were high compared to late onset of PE. In our study also sEnd levels median ± SE in late onset is 2127± 1660 and in early the onset median ± SE is 3134 ±11180 matches with the present study but with a sample size of 300 pregnant women[17]. In a study performed by Khalil *et al* proved that plasma levels of sEnd are a diagnostic marker in late gestational PE[18]. Another study performed in Indonesian population states that serum sEnd levels are a diagnostic marker in early onset PE[6]. The sEnd levels were significantly increased in severe PE with AUC of 0.94, a cut-off value of 20.4 and are a noble diagnostic marker in Iranian population for PE[19]. In the Italian population, a study was performed and states that sEnd levels are significant with AUC 0.88 and no difference in sEnd levels in early & late PE[20]. In the Egyptian population at 13 weeks of gestation, sEnd levels were increased in high exposure of PE subjects along with early onset PE. In Levine *et al* studies proved that sEnd levels can be an early investigative indicator in the Egyptian and American populations [21, 22]. A study was conducted by Lai *et al* and their observations revealed that sEnd levels were more significant at early gestational weeks. So the maternal sEnd levels can be an early prognostic marker[23]. In the Japanese population observed that sEnd levels can be a diagnostic marker in PE with mean significant levels of 60.9 ± 28.8 [24]. Cui *et al* piloted a study with 110 PE and 62 normotensive pregnant women observations were increasing sEnd levels are matching with the severity of PE and a similar study results was observed by Venkatesha *et al* also [25, 26].

From Northern part of India 3 studies were performed and only one study was piloted from southern part of India. Present study is initial study in south eastern part of India with 300 sample size. The details of these studies are as follows: In North India, Sachan *et al* from Lucknow performed on 30 subjects the study revealed that sEnd is a unique marker to evaluate diagnostic and prognostic accuracy in PE women with cut-off value e" 6.26 ng/mL. This present study matches with Sachan *et al* study by a similar range but in present study the range of sEnd concentration was 8 ng/ml with 300 sample size [27]. Duhan *et al* from Haryana conducted a study on 100 subjects in PE and normotensive pregnant women, sEnd levels range from 2.54 ng/ml to 7.06 ng/ml and the levels were significant in PE. The present study matches with the above studies with cut off value 8 ng/ ml and with more sample size[28]. In south India, Archana *et al* from Kanchi Tamil Nadu a study was analyzed on 35 pregnant women with increased serum sEnd levels in late-onset PE[29]. A study from Chandigarh by Agarwal *et al* conducted on sEnd levels ranges from 84.9±38.8 vs 13.2 ± 6.3ngml–1[5]. In Plasma s-Eng levels can be a useful predictive & diagnostic marker[30].Based on all these studies the present study states, sEnd levels are statistically significant in late PE and if the serum levels are e"8 ng/ml are prone to PE in south eastern part of India. The north Indian studies from Lucknow & Haryana, a south Indian study from Tamil Nadu states that sEnd is a diagnostic marker in PE. But a change in the present study is with 300 sample size. This stands the first study in south-east part of Karnataka, India.

CONCLUSION

To conclude sEnd levels were elevated in the PE pregnant women than normotensive pregnant women. If we relate the serum sEnd along with gestational stages of PE, in early stages of PE the maternal serum sEnd secretions were significantly elevated. So it can be used as an early predictor marker. In conclusion the maternal serum sEnd level can be a diagnostic marker for PE, especially in South- East part of Indian -Kolar population.

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Ethical clearance

Central Ethics committee of Sri Devaraj Urs Academy of Higher Education and Research Center with No: SDUAHER/KLR/CEC/61/2020-21 in Kolar, Karnataka,India.

Conflict of interest

None of the authors declare conflict of interest.

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