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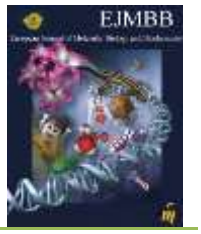

SERUM ENDOGLIN IN PREECLAMPSIA

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ABSTRACT
Background: Endoglin is a 180kDa homodimeric transmembrane glycoprotein consisting of 633 amino acids. It is a co-receptor of transforming growth factor TGF-β3. The soluble circulating form (sEng), cleared from membrane bound form (mEng) is an angiogenic factor, which was implicated in the pathogenesis of preeclampsia. Preeclampsia is characterized by high blood pressure (>140/90 mmHg), proteinuria (>300mg/day) after 20 weeks pregnancy in previously normotensive women. Aims and Objectives: To evaluate and compare the level of serum endoglin in preeclamptic women and healthy pregnant women and to correlate serum endoglin levels with blood pressure. Material and Methods: Study type: Case-control study conducted in the Department of Biochemistry and Department of Obstetrics and Gynaecology, RIMS Imphal Sample size: 30 preeclamtics and 30 healthy pregnant women admitted in antenatal ward, RIMS Study period:2 years Method: Serum Endoglin measured by ELISA method. Statistical analysis was done using SPSS version 21. P-value <0.05 was considered significant Results: Serum endoglin was found to be higher in cases(14.28±4.09) ng/ml than in controls (7.30±1.12)ng/ml. The levels were found to be positively correlated with both systolic and diastolic BP(r=0.819) and r=0.861 respectively) and were statistically significant(p=0.000) Conclusion: It was evident from the study that the mean serum endoglin levels were higher in preeclamptic women so it has the potential to be used as a new diagnostic biomarker of preeclampsia and as a predictor of disease severity.

INTRODUCTION

Hypertensive disorders in pregnancy (HDP) are one of the leading causes of maternal mortality and stillbirths. [1] Preeclampsia (PE), a pregnancy specific syndrome characterized by new onset hypertension and proteinuria develops during the second half of pregnancy and remits after delivery or termination of the pregnancy, suggesting that the placenta is a central culprit in the disease. [2] It is diagnosed as blood pressure (BP) of ≥ 140 mmHg systolic or ≥90mm Hg diastolic on two occasion atleast 4 hours apart after 20 weeks gestation in previously normotensive women and proteinuria ≥300mg per 24hours urine collection or ≥+1 by dipstick method.[3] The incidence of preeclampsia is about 5-7% of all pregnancies.[4].

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%).[5] In India it is around 10% and United States of America it is 2.5%.[6]

The pathophysiology of preeclampsia remains undefined, placental ischemia or hypoxia is widely

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regarded as a key factor.[7] Inadequate trophoblast invasion leads to incomplete remodelling of the uterine spiral arteries and this is considered as the primary cause of placental ischemia.[8] It has been postulated that the resultant poor placentation and reduced placental perfusion in early pregnancy leads to release of number of factors into the maternal circulation which causes systemic endothelial cell dysfunction, intravascular inflammation and multiple organ damage.[9] These factors include the cytokines, syncytiotrophoblast microparticles, apoptotic products, reactive-oxygen species, activated leukocytes, angiotensin II type I receptor antibody, soluble vascular endothelial growth factor receptor (sVEGFR)-I, soluble forms like tyrosine kinase (sFlt) and soluble endoglin (sEng).[10]

Endoglin is a 180kDa homodimeric transmembrane glycoprotein consisting of 633 amino acids.[11] It is a cell surface co-receptor of transforming growth factor TGF-βI and TGF-β3 and is highly expressed on endothelial cells, syncytiotrophoblasts, endometrial stromal cells, monocytes and hematopoietic stem cells.[12] sEng (soluble circulating form) is produced by the proteocleavage of the placental-membrane bound form (mEng) by the action of membrane bound matrix metalloproteinase-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.[13] Endoglin regulates TGF-β signalling pathway by interacting with TGF-βI and II, and acts as a pro-angiogenic factor by regulating nitric oxide dependant vasodilation. It plays a role in vascular tone maintenance and probably control placental implantation and spiral artery remodelling during pregnancy.[14]

Various studies have shown that endoglin plays an important role in the pathogenesis of preeclampsia, however no study has been conducted in this part of India. So, this study is planned to evaluate the serum level of endoglin in preeclampsia and assess whether there is any association between serum endoglin levels and pregnancy outcome in preeclampsia.

MATERIALS AND METHODS

Study design:

Case-control study

Study setting:

Conducted in the Department of Biochemistry in collaboration with Department of Obstetrics and Gynaecology, RIMS, Imphal

Study duration:

The study was carried out for a period of 24 months from 0ctober 2018 to September 2020

Study population: 30 preeclamptics and 30 healthy pregnant women admitted in antenatal ward, RIMS

Inclusion Criteria:

Patients considered as cases were preeclamptic women aged 18 years and above, admitted in antenatal ward and willing to participate in the study and patients considered as controls were normotensive pregnant women with no proteinuria admitted in antenatal ward.

Exclusion Criteria: Chronic hypertension, diabetes mellitus, multiple pregnancies, renal disease, smokers, neoplastic diseases

Measurement of Serum endoglin levels: Measured by Enzyme Linked Immunosorbent Assay (ELISA) as described by Portstmann T and Kiessig ST [15] using Human Endoglin (ENG)ELISA cat no K12-3704 manufactured by KinesisDX, USA

Statistical analysis: was done using SPSS version 21. p-value <0.05 was considered significant.

RESULTS:

Table 1: Shows the mean ± SD of serum endoglin was found to be higher in cases as compared to controls and the difference was statistically significant at p=0.000.

Study groups(N)	Serum Endoglin (ng/ml) Mean±SD	p-value
Cases(30)	14.28 ± 4.09	0.000
Control(30)	7.03 ± 1.12	

Table 2: Shows the positive correlation between serum endoglin and systolic blood pressure among the cases and statistically significant at p=0.000

Parameters	Pearson correlation (r)	p-value
SBP	0.819**	0.000

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

Table 3: Shows positive correlation between serum endoglin and diastolic blood pressure among cases and statistically significant at p=0.000

Parameters	Pearson correlation(r)	p-value
DBP	0.861**	0.000

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

Table 4: Depicts higher value of serum endoglin was observed in women who gave birth to preterm babies. Women who delivered by C-section had higher levels of serum endoglin. Mean serum endoglin was higher in in women who delivered LBW babies and the women who had stillbirth and had complications had higher levels of serum endoglin levels.

Pregnancy outcome	N(30)	Endoglin (ng/ml) Mean ± SD	p-value
Gestational age at delivery(weeks)			
Term	11	10.2 ± 2.18	0.000
Preterm	19	16.7 ± 2.81	
Modes of delivery			
Vaginal	18	12.8±2.78	0.02
Caesarean	12	16.5±4.77	
Birth weight			
LBW	10	17.1±2.84	0.000
Normal	20	16.5±4.77	
Birth outcome			
Stillbirth	3	19.3±1.21	0.000
Livebirth	27	13.0±3.53	
Maternal complications			
No	17	11.3±2.38	
Yes	13	18.1±1.99	0.000
Maternal Death			
No	27	13.4±3.77	0.004
Yes	3	19.5±1.29	

***p < 0.05 is considered to be statistically significant**

DISCUSSION

It is evident from Table 1, that the values of serum endoglin levels were two fold higher as compared to controls. The findings were supported by the results of the study by Sachan R et al[16] who found that the levels of serum endoglin in severe preeclampsia was seven times higher than in normal controls. The exact pathophysiology of preeclampsia is unknown but generalised endothelial dysfunction with systemic inflammatory response (SIRs) is thought to be the 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 tyrosine kinase 1(sFlt-1) and soluble endoglin are involved in placental vascular development.[13] Soluble endoglin rises during normal as well as in preeclamptic pregnancy but 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 levels among cases and the findings were found to be statistically significant as seen in table 2 and table 3 which was also supported by study conducted by Elhawary TM et al.[17] This can be explained by the fact that serum endoglin blocks the TGF-β1 mediated activation of endothelial nitric oxide synthase (eNOS) leading to 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 vessels healthy. Due to this antagonistic effect cell lining of the blood vessels begin to sicken and die, and this change might be responsible for the increase in blood pressure and proteinuria.[18,19] It is well known 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.

Table 4 depicts that the serum endoglin levels was higher in the mothers who showed bad pregnancy outcomes. Levels were also higher in mothers who gave birth to preterm babies than the mothers who delivered term babies. The levels of serum endoglin were even higher in mothers who delivered stillbirths and LBW babies. The values were found to be statistically significant. Placental ischemia which is thought to lead to fetal and placental distress, resulting in fourfold increase expression of mEng[13] and also increase in sEng levels which can enhance vascular permeability and reduce placental perfusion by damaging the integrity of endothelial cells.[20] Maternal outcomes were also analysed among the cases and it was seen that 13 out of 30 cases had maternal complications live HELLP syndrome, renal failure, postpartum haemorrhage. The mean values of serum endoglin were higher in the women who had complications (18.1±1.99) ng/ml than the women with no complications (11.3±2.38)ng/ml among the cases. In the

present study, 3 maternal deaths were observed among the cases and the mean serum endoglin levels were also significantly higher in mothers who expired as compared to other cases who survived the disease i.e (19.5±1.29 and 13.4±3.77)ng/ml respectively. These findings imply that higher serum endoglin levels are associated with higher morbidity and mortality, thus indicating its contribution to the severity of the disease. These findings were supported by study conducted by Rana S et al [21] who demonstrated that the levels of serum endoglin were higher in women with adverse maternal outcome.

CONCLUSION

In this study serum endoglin levels were increased with increased blood pressure and the correlation was statistically significant. It was also found that with the increased levels of serum endoglin in cases, the adverse pregnancy outcomes were observed and the findings also statistically significant. From above results, it was concluded that serum endoglin could be a potential diagnostic biomarker of preeclampsia and could predict the severity of the disease.

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