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Association of Serum Soluble Endoglin Levels with Adverse Foetomaternal Outcome in Preeclampsia and Eclampsia

Rekha Sachan[1*], Munna Lal Patel[2], Pratima Verma[1], Soniya Dheeman[1] and Pooja Gupta[1]

[1]Department of Obstetrics and Gynaecology, King George Medical University, U.P, Lucknow, India.
[2]Department of Medicine, King George Medical University, U.P, Lucknow, India.

Authors' contributions

This work was carried out in collaboration between all authors. Author RS designed the study, wrote the protocol and wrote the first draft of the manuscript. Author MLP managed the literature searches and analyses of the study. Author SD performed the Endoglin estimation and data collection and analysis. Authors PV and PG helped in final manuscript preparation and revision. All authors read and approved the final manuscript.

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ABSTRACT

Background: Serum Endoglin has also previously shown to be elevated in woman with established preeclampsia especially in those presenting with preterm labour and foetal growth retardation.
Objectives: To evaluate association of serum soluble Endoglin with adverse foeto-maternal outcome in woman with hypertensive disorders of pregnancy.
Materials and Methods: A prospective case control study carried out from 2013 to 2014 at department of Obstetrics and Gynaecology. Ethical clearance was obtained from institutional ethics committee No.ECR/262/Inst/UP/2013 from King Georges Medical University, Lucknow. After informed consent, total 90 pregnant women from gestational age 20-40 weeks were enrolled after

**Corresponding author: E-mail: drrekhasachan@gmail.com;*

randomization. 30 women of preeclampsia and 30 of antepartum eclampsia served as cases where as 30 normotensive pregnant women served as controls. Preeclampsia was defined as per NHBPEP2000 working group. Estimation of serum soluble Endoglin level was done by Enzyme linked immunosorbent assay using ELISA kit.

Results: Serum Endoglin levels were found higher in preeclampsia and eclampsia group ($p<0.001$) in comparison to controls. The women who had complication in terms of postpartum haemorrhage, cerebrovascular accident during the study had maternal serum Endoglin levels 12.48 ng/ml, and 16.08 ng/ml, respectively in preeclampsia group and 15.88 ng/ml, 16.76 ng/ml respectively in eclampsia group. 4 women expired, all were from eclampsia group mean serum Endoglin level of these women was 14.18±2.4. Serum Endoglin levels increased with low birth weight in preeclampsia and eclampsia. 12 neonates in preeclampsia and 17 neonates in eclampsia, required admission to NICU, in whom the maternal serum Endoglin level was 14.67±1.77, 15.68±1.48 respectively, which was higher than those neonates who did not required admission & difference was statistically significant ($p<0.001$). Neonates who died had high maternal S. Endoglin level (15.77±0.44 and 16.23±1.30) as compared to alive foetuses (12.35±2.49, 14.30±1.86 respectively).

Conclusion: Serum soluble Endoglin level might predict adverse foetomaternal outcome, but larger studies should be carried out to confirm this association.

Keywords: Serum endoglin; preeclampsia; eclampsia; pregnancy outcome; fetal outcome.

1. BACKGROUND

Preeclampsia is a common complication of pregnancy affecting 5-8% of all pregnant women [1]. It seems to be precipitated by the release of circulating factors from the placenta that induces endothelial dysfunction like Endoglin, and vascular endothelial growth factor (VEGF), etc. Evidence suggests that the endothelial dysfunction is the central mechanism in the pathogenesis of preeclampsia. The exact cause for endothelial dysfunction is not yet clear but poor placentation has been described as a major factor [2]. Soluble anti angiogenic factor like serum soluble endoglin is secreted in excess by the placenta in the maternal circulation in Preeclampsia.

Endoglin is a homodimeric transmembrane glycoprotein which is accepted as co receptor for transforming growth factor beta (TGF B) [3]. This might be responsible for endothelial dysfunction and clinical signs of preeclampsia. Serum Endoglin inhibits endothelial function in vitro and administration of Endoglin induces hypertension in vivo. The combined administration of serum Endoglin and vascular endothelial growth factor receptor-1(VEGFR-1) (anti angiogenic factor) to pregnant rats induces hypertension, proteinuria and foetal growth restriction [4]. Serum Endoglin has also been previously shown to be elevated in woman with established preeclampsia especially in those presenting with preterm labour and foetal growth retardation. So it may also be associated with other adverse fetomaternal outcome in preeclampsia. There is paucity of data demonstrating clinical utility of serum soluble Endoglin in preeclamptic women with adverse foetomaternal outcome [5,6,7].

Thus this study was planned to evaluate the association of serum soluble endoglin with adverse foetal and maternal outcome in women with hypertensive disorders of pregnancy.

2. MATERIALS AND METHODS

This is a prospective case control study carried out over a period of one year from June 2013 to August 2014 in department of Obstetrics and Gynaecology, King George Medical University, Lucknow. After informed consent and ethical clearance from institutional ethics committee, a total of 90 pregnant women with gestational age 20 -40 weeks were enrolled. Thirty women of preeclampsia and 30 of antepartum eclampsia served as cases, 30 normotensive pregnant women served as controls, the controls adjusted by gestational age with the cases. Preeclampsia was defined as per NHBPEP2000 working group; resting hypertension >140/90 mmHg after 20 weeks of pregnancy and proteinuria >300 mg/24 hours. Eclampsia was defined as Preeclampsia with seizures.

Women with multiple pregnancy, chronic kidney disease, liver disease, cardiovascular disease, collagen vascular disease, chronic hypertension, diabetes, neoplasm or with major foetal anomaly and with history of smoking and alcohol were

excluded from the study. During this study period after admission Blood pressure and labour were strictly monitored. All patients were given antihypertensive drugs however, mild preeclampsia cases, were treated by Methyldopa and in severe preeclampsia, the patients were treated with Labetalol. Methyldopa is a centrally acting US Food and Drug Administration category B drug considered safe for the mother and fetus. Labetalol, a Food and Drug Administration category C drug, was given in cases of severe preeclampsia and eclampsia. Magnesium sulfate, according to the Pritchard regimen, was administered to control convulsions in patients with eclampsia, along with fluid replacement in addition, patients with eclampsia were intensively monitored. Injection dexamethasone 6mg intramuscular 12 hourly a total 4 dose was administered to achieved the lung maturity of foetus.

3. METHODOLOGY

5 ml of venous blood sample was collected from cases and controls and centrifuged at 6000 rpm for 5 minute and serum was stored at -20℃ until assay. Estimation of serum soluble Endoglin level was done by Enzyme linked immunosorbent assay using ELISA kit manufactured by USCNK life science inc. Adverse maternal outcome was defined in terms of occurrence of delivery by caesarean section, preterm delivery and complications like, abruption, cerebrovascular accident and last maternal deaths.

Adverse foetal outcome was defined as Low birth weight, Intrauterine death, low APGAR score, neonatal resuscitation, NICU admission and finally neonatal deaths. APGAR score test is generally done at one and five minutes after birth, scores 7 and above are normal, 4 to 6 fairly low, and 3 and below are generally regarded as critically low.

3.1 Ethical Approval

Ethical clearance was obtained from institutional ethics committee (No.ECR/262/Inst/UP/2013) from King Georges Medical University, Lucknow.

3.2 Statistical Analysis

The statistical analysis was done by using SPSS (Statistical package for social sciences) version 15.4. The categorical data was described as n (%) and continuous variable as mean+- SD. ANOVA (analysis of variance) test was used to compare within the group and between the group variances amongst the study group. ANOVA provide 'F' ratio, whereas a higher 'F' value depicted a higher intergroup differences. Serum Endoglin levels were adjusted for gestational age by regression analysis. Student-t test was used to test the significance of two means. p value <0.05 considered significant.

4. RESULTS

Total number of admissions was 14,295 and out of this total number of deliveries were 8,646. So delivery rate in this year was 60.48%.

We found higher level of mean serum Endoglin in eclampsia (14.96±1.96) cases as compared to preeclampsia cases (10.21±0.86) but difference was statistically significant (P <0.001).

4.1 Association of Serum Endoglin Level with Foetal Outcome

As the foetal birth weight increased, the serum Endoglin levels decreased in all the three groups or in other words it can be postulated that serum Endoglin levels increased with low birth weight in preeclampsia and eclampsia group. Mean maternal serum Endoglin level was 10.60±1.61 with birth weight more than 2.5 kg and 14.37±1.84 with birth weight 2-2.5 kg and increased to 14.91±1.10 with birth weight less than 2 kg in preeclampsia group. In eclampsia mean S. Endoglin level was 13.99±1.94 with birth weight of >2.5 kg and 15.48±1.98 with birth weight of 2-2.5 kg and 15.58±1.54 with birth weight less than 2 kg.

Even in control group slight increase in serum Endoglin level (2.05±0.96) with birth weight of 2-2.5 kg was observed as compared to birth weight >2.5 kg (2.05±0.53) (Table 1).

Women in eclampsia group were admitted with foetal demise all of them had higher serum soluble Endoglin level (17.01±1.10), as compared to those who had live pregnancy (14.73±19.1), these levels are almost double as compared to controls (serum Endoglin level of 9.62±5.87) (Table 2).

Those neonates who delivered with low APGAR score in preeclampsia and eclampsia group had higher maternal serum Endoglin levels as compared to those who had normal APGAR score. The intergroup comparison of maternal

serum Endoglin level amongst low APGAR and normal APGAR score foetuses was found to be statistically significant (p<0.001). On the other hand in controls maternal serum Endoglin level was slightly lower who had low APGAR score neonates as compared to normal APGAR score neonates (Table 3).

A total of 7 neonates in preeclampsia and 14 neonates in eclampsia group required resuscitation and all those women who had these neonates had higher mean serum Endoglin level (15.33±0.60 and 15.69±1.43 respectively) as compared to those who did not require resuscitation (11.74±2.32 and 13.69±1.86 respectively) (Table 3). A total of 12 neonates required admission to NICU in preeclampsia group in whom the mean maternal serum Endoglin level was 14.67±1.77.

Seventeen neonates in eclampsia group were admitted in NICU who had mean maternal serum Endoglin level 15.68±1.48 which was higher than those neonates who did not required admission, thus this difference was statistically significant (p<0.001) (Table 3). According to literature fetal lung maturity usually occur at gestation age 32 to 34 weeks and in preeclampsia it occurs 1 to 2 weeks prior. In present study out of 30 eclampsia, 23 patients had foetus of 35 to 40 weeks of gestation and they had achieved lung maturity spontaneously. Out of rest 7 patients 2 patients admitted with intrauterine foetal demise and only 5 patients were admitted between gestational age of 28 to 34 weeks.

A total of 2 neonatal deaths occurred in preeclampsia group and 6 neonatal deaths occurred in eclampsia group. Neonates who died had higher maternal mean serum Endoglin level (15.77±0.44 in preeclampsia group and 16.23±1.30 in eclampsia group) as compared to alive foetuses (12.35±2.49 and 14.30±1.86 respectively) (Table 2).

Table 1. Association of Serum soluble Endoglin level with neonatal birth weight

SN	Variable	Total (n=90)		NP (n=30)		PE (n=30)		E (n=30)		Significance (Inter group)
		n	Mean± SD	N	Mean± SD	n	Mean± SD	n	Mean± SD	
1.	Birth weight									
	<2.0 kg	12	15.30± 1.36	0	-	5	14.91± 1.10	7	15.58± 1.54	F=0.69; p=0.426
	2-2.5kg	25	13.46± 4.59	3	2.32± 0.96	10	14.37± 1.84	12	15.48± 1.98	F=62.499; p<0.001
	>2.5 kg	53	6.95± 5.33	27	2.05±0.53	15	10.60± 1.61	11	13.99± 1.94	F=427.76; p<0.001
	Significance (Within group)	F=24.532; p<0.001		F=0.604; p=0.443		F=22.15; p<0.001		F=2.316; p=0.118		

Table 2. Association of serum soluble Endoglin level with still birth analysis

SN	Variable	Total (n=90)		NP (n=30)		PE (n=30)		E (n=30)		Significance (Inter group)
		N	Mean± SD	N	Mean± SD	n	Mean± SD	n	Mean± SD	
2.	IUD									
	No	87	9.62± 5.87	30	2.08± 0.56	30	12.57± 2.56	27	14.73± 1.91	F=381.87; p<0.001
	Yes	3	17.01± 1.10	0	-	-	-	3	17.01± 1.10	-
	Significance (Within group)	t=2.164; p=0.033		-		-		t=2.007; p=0.054		
5.	Neonatal death									
	Yes	8	16.11± 1.13	0		2	15.77± 0.44	6	16.23± 1.30	F=0.216; p=0.658
	No	79	8.97± 5.76	30	2.08± 0.56	28	12.35± 2.49	21	14.30± 1.86	F=363.13; p<0.001
	Significance (Within group)	t=3.484; p=0.001		-		t=1.910; p=0.066		t=2.358; p=0.027		

IUD-intrauterine foetal demise

Table 3. Association of serum soluble Endoglin level with requirement of neonatal resuscitation

SN	Variable	Total (n=90)		NP (n=30)		PE (n=30)		E (n=30)		Significance (Inter group)
		N	Mean± SD	N	Mean± SD	n	Mean± SD	n	Mean± SD	
3.	Apgar score									
	Low	47	13.14± 4.09	4	1.96± 0.49	18	13.36± 2.51	25	14.78± 1.98	F=61.883; p<0.001
	Normal	40	5.49± 4.89	26	2.09± 0.58	12	11.40± 2.24	2	14.10± 0.65	F=251.35; p<0.001
	Significance (Within group)		t=7.957; p<0.001		t=0.423; p=0.676		t=2.179; p=0.038		t=0.475; p=0.639	
4.	Resuscitation needed									
	Yes	21	15.57± 1.21	0		7	15.33± 0.60	14	15.69± 1.43	F=0.403; p=0.533
	No	66	7.73± 5.49	30	2.08± 0.56	23	11.74± 2.32	13	13.69± 1.86	F=333.60; p<0.001
	Significance (Within group)		t=6.469; p<0.001		-		t=4.010; p<0.001		t=3.146; p=0.004	
6.	NICU admission									
	Yes	29	15.26± 1.66	0		12	14.67± 1.77	17	15.68± 1.48	F=0.403; p=0.533
	No	58	6.80± 5.14	30	2.08± 0.56	18	11.18± 1.99	10	13.11± 1.43	F=333.603; p<0.001
	Significance (Within group)		t=8.614; p<0.001		-		t=4.902; p<0.001		t=4.417; p<0.001	

4.2 Association of Serum Endoglin with Maternal Outcome

Serum Endoglin levels were found higher in preeclampsia and almost 7 times in eclampsia group (p<0.001) in comparison to controls.

There were more number of normal deliveries in control group as compared to preeclampsia and eclampsia. All preterm deliveries were reported in preeclampsia and eclampsia group.

After analysis of mode of delivery, women who had full term normal vaginal delivery in all three groups had lower levels of serum soluble Endoglin as compared to those who had undergone caesarean delivery. After inter group comparison women who had full term normal vaginal delivery, the mean serum Endoglin level was lowest in controls and highest in eclampsia, the difference was statistically significant. (p<0.001)In those women who had undergone LSCS, mean serum Endoglin level was highest in eclampsia group and lowest in controls, this difference was also statistically significant (p<0.001) (Table 4).

Women who had preterm vaginal delivery (2 in preeclampsia and 3 in eclampsia group) had higher level of serum Endoglin as compared to those women who had full term vaginal delivery within the same group (Table 4).

Maternal complication analysis revealed that 1 patient in preeclampsia and 1 in eclampsia group had postpartum haemorrhage and serum Endoglin level was 12.48 ng/ml and 15.88 ng/ml respectively.

1 woman in preeclampsia and 1 in eclampsia group suffered with cerebrovascular accident and had serum Endoglin level 16.08 ng/ml and 16.76 ng/ml respectively. 3 women in preeclampsia and 5 in eclampsia group suffered with abruption and mean Endoglin level was 15.35±0.70 and 16.33±0.63 respectively.

A total of 4 women deceased during the study period and all were from eclampsia group mean serum Endoglin level of these women was 14.18±2.4 (Table 5). 4 women out of 30 with eclampsia deceased. One because of pulmonary embolism, second because of adult respiratory distress syndrome, third and fourth death because of cerebrovascular accidents. All maternal mortalities were due to complications following eclampsia.

Table 4. Association of serum soluble Endoglin level with mode of delivery

SN	Variable	Total (n=90)		NP (n=30)		PE (n=30)		E (n=30)		Significance (Inter group)
		n	Mean± SD	N	Mean± SD	n	Mean± SD	n	Mean± SD	
3.	Mode of delivery									
	FTND	26	8.55± 55.84	11	2.22± 0.57	6	11.99± 2.83	9	14.00± 1.98	F=121.95; p<0.001
	LSCS	59	10.04± 5.99	19	1.99± 0.56	22	12.71± 2.46	18	15.27± 1.98	F=264.95; p<0.001
	PTVD	5	14.71± 2.91	0	-	2	12.87± 4.54	3	15.94± 1.00	F=1.500; p=0.308
	Statistical Significance (Within group)	F=2.406; p=0.096		F=1.140; p=0.295		F=0.188; p=0.829		F=1.758; p=0.192		

- *FTND-full term normal delivery, LSCS-lower segment caesarean section, PTVD-preterm vaginal delivery. p<0.05 statistically significant*

Table 5. Association of serum soluble endoglin level with maternal complication

SN	Variable	Total (n=90)		NP (n=30)		PE (n=30)		E (n=30)		Significance (Inter group)
		n	Mean± SD	N	Mean± SD	n	Mean± SD	n	Mean± SD	
4.	Maternal complications									
	PPH	2	14.18± 2.40	0		1	12.48	1	15.88	-
	CVA	2	16.42± 0.48	0		1	16.08	1	16.76	-
	Abruption	8	15.96± 0.79	0	-	3	15.35± 0.70	5	16.33± 0.63	F=4.276; p=0.084
	Mortality	4	14.18± 2.40	0	-	-	-	4	14.18± 2.40	-
	$MgSO_4$ need	44	14.86± 1.81	0	-	14	14.66± 1.48	30	14.96± 1.96	F=0.248; p=0.621

Thus after analysis it was found that more complications and maternal deaths were reported in eclampsia group as compared to preeclampsia group. Mean serum Endoglin level was also higher with every type of complication in eclampsia group as compared to preeclampsia group. The highest level of serum Endoglin was found in patient with cerebrovascular accidents. No complications occurred in control group.

5. DISCUSSION

We found that Serum soluble Endoglin was elevated in patients with preeclampsia and eclampsia. We also wanted to evaluate whether it stands out as effective marker alone in detecting adverse maternal and foetal outcome in such patients. Various clinical studies [8,9,10] have shown that it is challenging to predict adverse outcome in women with preeclampsia. It has been found that increased level of serum soluble Endoglin are associated with adverse antenatal and postnatal complications. Sarosh Rana et al. [11] also reported that levels of plasma Endoglin were higher in woman who experienced any adverse outcome as compared to women who did not. In the subgroup analysis they found levels of plasma Endoglin were higher in women with, elevated liver function test (LFT), low platelet count, small for gestation age neonates and abruption, compared to women with no adverse outcome.

It is now well established that vascular endothelial dysfunction is the principal event in the pathophysiology of preeclampsia [11]. As per our study poor foetal outcome was observed in terms of low birth weight neonates, pre term delivery, intra uterine foetal death and neonatal death, increased neonatal intensive care unit admission with low APGAR score babies. We found that mean maternal serum soluble Endoglin levels were higher in preeclampsia and eclampsia group with adverse foetal outcome. Similarly reported by Elhawary et al. [11] In our study maternal serum soluble Endoglin level were seven fold increased with low birth weight babies as compared to Sarosh Rana et al. [12] who found ten fold increase in Endoglin with growth restricted foetus.

Venkatesha et al. [4] also reported that exogenous soluble Endoglin administration in pregnant rats lead to development of severe pre eclampsia, foetal growth restriction and HELLP syndrome. They suggested that serum soluble Endoglin increased the likelihood of HELLP syndrome in rat model as well as in human preeclampsia.

On the other hand Lee et al. [13] also reported that soluble fms-like tyrosine kinase I and soluble Endoglin are useful to diagnose preeclampsia but the serum level of these factors may not correlate with poor pre natal outcome.

Yet other studies have reported that elevated Endoglin may be a mechanism in other obstetric syndromes as well, such as foetal death and small for gestational age neonates [14,15].

Romero et al. [16] had reported that patients destined to deliver small for gestational age neonates had higher concentration of Serum Endoglin throughout gestation than those with normal pregnancies.

Even Levine et al. [5] reported that normotensive patients who later delivered SGA neonates had higher maternal serum soluble Endoglin compared to controls at 17 to 20 weeks of gestational age. Similar observation were also seen in our study, even maternal serum soluble Endoglin of control group was higher in those who delivered low birth weight baby as compared to those who delivered normal weight baby.

We observed that maternal Serum endoglin levels were significantly higher in mothers of those neonates who had low APGAR score at birth, required resuscitation, admission in NICU and neonatal deaths. Mean serum Endoglin was highest among mothers who had still birth, which is one of the worst outcome of pregnancy.

Others studies had only reported adverse relationship of SGA foetus with Endoglin levels. In our study we observed that increasing serum Endoglin levels were associated with lower birth weight of baby, or inverse relationship was found between serum soluble Endoglin levels and neonatal birth weight.

Maternal Serum Endoglin levels were found to be higher in mothers who underwent preterm delivery in the present study.

It is well known fact that quite often we have to terminate preterm pregnancy to save life of mother as well as foetus in case of precclampsia and eclampsia. But now serum Endoglin is emerging as a sensitive and reliable marker to predict adverse fetal outcome. We can safely prolong pregnancy with significant foetal benefit by estimating maternal serum endoglin level.

Postpartum haemorrhage (PPH), cerebrovascular accident (CVA) and abruption are one of the worst complications of eclampsia as reported in our previous study [17]. To best of my knowledge no study has yet been reported in PUBMED to established association of serum soluble Endoglin level with adverse maternal outcome in detail in preeclampsia and eclampsia except Sarosh Rana et al,. In our study it was found that serum Endoglin levels were significantly raised in women who suffered with PPH, abruption, cerebrovascular accident in comparison to those who did not. Maternal mortality is the terminal outcome of any obstetrical complication of pregnancy. We found significantly higher serum Endoglin levels in mothers who died as compared to those who were alive. Serum Endoglin was directly associated with maternal mortality indicated its utility in prediction of this outcome.

Sarosh Rana et al. [12] compared Endoglin alteration in women with preeclampsia especially in those presenting pre mature delivery or in mother carrying a growth restricted foetus and prediction of adverse maternal and neonatal outcome was done within two weeks of presentation. Plasma Endoglin level were higher in women who experienced any adverse outcome as compared to women who did not.

As per various studies after evaluation of overall adverse foetomaternal outcome, Yadav et al. [18] reported overall perinatal mortality 14.8% and preterm delivery 28.8% in preeclampsia, but in our study we found overall perinatal mortality 12.2%. Perinatal mortality was highest among eclampsia in our study similar to Perloff et al. [19] study.

Overall maternal mortality was 2.8% and highest maternal mortality was observed in eclampsia group i.e. 8.89% in our previous study [17] in contrast to 17-18% in other study [20,21]. Whereasas in the present study we found overall maternal mortality was 4.44% and all deaths reported in eclampsia group i.e.13.3%. Author of one study reported that an increased plasma sEng concentration in preeclampsia is associated with abnormalities in uterine and/or umbilical artery Doppler velocimetry [22]. Here we want to emphasize that even after

improvement in maternal and child health care facilities, the rate of maternal and neonatal mortality can be changed even a little in our study. Unfourtunately because of illiteracy, lack of awareness and poor antenatal care in rural areas, these cases were admitted in the emergency after the development of eclampsia in late stages. There is a need to strengthen good neonatal intensive care in addition to labor monitoring and expeditious delivery is required for better outcomes in cases of severe preeclampsia and eclampsia.

There is a need to find out a marker like Endoglin that can predict these worst foetal and maternal outcome even at an early stage. To establish the role of Serum Endoglin in management of these women in future needs larger study.

6. CONCLUSION

The association of elevated endoglin levels and impaired maternal and fetal outcome was observed in this study and serum endoglin might be a sensitive screening method for severe cases. Nowadays better intensive care unit and use of MgSO4 and availability of injection labetolol there is definite improvement in management of women suffering with preclampsia and eclampsia. This marker can be used to prevent preterm induction in preeclampsia and eclampsia as it is independently associated with adverse foetomaternal outcome.

Thus estimation of serum soluble endoglin level even at advanced gestational age could be used as a sensitive screening method to predict adverse foetomaternal outcome in preeclampsia or eclampsia or in other words this could help to improve pregnancy outcome in such type of patients.

This indicate that serum endoglin level provide prognostic information besides clinical presentation and incorporation of this marker, may allow identification of patient at risk for adverse outcome necessitating timely transfer to tertiary care centre, and administration of steroids, thus reducing unnecessary admission and intervention. Larger studies are still required for recommending routine estimation of serum soluble Endoglin for assessing adverse foetomaternal outcome.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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