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Evaluation of Serum level of thrombomodulin in cases with preeclampsia

Hayam F. Mohammed[1,*], Yasser M. Abou Taleb[1], Nashwa N. El-Khazragy[2], Sohaila K. Ahmed[1], Rehab M.Abdelrahman[1]
[1]Departments of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, Cairo, Egypt
[2]Departments of obstetrics and Clinical Pathology/Hematology, Faculty of Medicine, Ain Shams University, Cairo, Egypt

SUMMARY

AUTHORS' CONTRIBUTION: (A) Study Design · **(B)** Data Collection . **(C)** Statistical Analysis · **(D)** Data Interpretation · **(E)** Manuscript Preparation · **(F)** Literature Search · **(G)** No Fund Collection

Background: Preeclampsia is a multisystmic disorder of unknown cause. Endothelial cell damage has recently been suggested to underlie the pathologic change in preeclamptic pregnancy. Thrombomodulin an endothelial cell surface glycoprotein act as a co-factor for thrombin catalyzed activation of protein C. activated protein C inhibits coagulation by inactivation the coagulation factor Va and VIIIa.

Aim of the Work: to assess the changes in thrombomodulin level in women with preeclampsia. Patients and Methods: This prospective case-control study was conducted on 123 women at Ain Shams University Maternity Hospital.

Results: Regarding clinic-pathological features of pre-eclampsia patients and healthy control groups, our study found that there was high significant difference (p≤0.01) between hypertensive and normal patients regarding (hypertension, obesity and history of PET). Our study found that there was high significant difference (p≤0.01) between pre-eclampsia patients and healthy control group regarding serum thrombomodulin protein level and serum thrombomodulin protein increases significantly with mild and severe preeclampsia and HELLP syndrome and considered a good marker for evaluation of hypertensive patients with pregnancy.

Conclusion: Serum thrombomodulin protein level is considered a good marker for evaluation of hypertensive patients with pregnancy.

Keywords: Uterine leiomyoma; Vitamin D

Address for correspondence:

Dr. Hayam F. Mohammed,
Departments of obstetrics and Gynecology, Faculty of Medicine,
Ain Shams University, Cairo, Egypt
E-mail: passanthamza81@outlook.com

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INTRODUCTION

Preeclampsia is a multisystemic disorder of unknown cause. Endothelial cell damage has recently been suggested to underlie the pathologic change in preeclamptic pregnancy. Thrombomodulin an endothelial cell surface glycoprotein act as a co-factor for thrombin catalyzed activation of protein C. activated protein C inhibit coagulation by inactivation the coagulation factor Va and VIIIa [1].

Pre-eclampsia (PE) is a pregnancy specific, multisystem disorder characterized by reduced organ perfusion secondary to diffuse endothelial injury [2].

The condition complicates about 3-6% of pregnancies worldwide. Despite extensive research, the exact etiology of pre-eclampsia remains elusive [3]. Severe preeclampsia is associated with increased risk of maternal mortality (0.2%) and increased rates of maternal morbidity (5%) such as convulsions, pulmonary edema, acute renal or liver failure, liver hemorrhage, disseminated intravascular coagulopathy (DIC), and stroke. These complications are commonly seen in women with preeclampsia that develops before 28 weeks (early onset PE) gestation and in those with preexisting medical conditions [4].

Serum uric acid levels have been reported to be significantly elevated in subjects with preeclampsia in many studies. Some authors suggest that the degree of elevation correlates with the severity of the maternal syndrome and of fetal morbidity [5].

Lactate Dehydrogenase (LDH) levels were significantly elevated in women with preeclampsia and eclampsia. Higher LDH levels had significant correlation with high blood pressure as well as poor maternal and perinatal outcome [6].

Thrombomodulin (TM); is a cell surface-expressed transmembrane glycoprotein which was originally identified on vascular endothelium. It acts as a natural anticoagulant. Endothelial injury results in TM release [7].

Thrombomodulin is a critical cofactor in the initiation of the protein C (PC) anticoagulant pathway. Plasma levels of thrombomodulin are regulated on a genetic basis, but more important is the dependence on a series of other atherosclerotic risk factors, such as hypertriglyceridemia, stroke, cancer, and diabetes [8]. In normal pregnancy, activation of platelets and release of thromboglobulin and platelet factor 4 are documented. Increased expression of thrombo-modulin is now considered an independent risk factor for vascular disease [9].

AIM OF THE WORK

To detect that if there is significant relation between the serum level of thrombomodulin and degree of severity of cases of preeclampsia.

PATIENTS AND METHODS

This A prospective case-control study was conducted on Department of Obstetrics & Gynecology & Ain shams University maternity hospital.

Study population

Women attending hospital antenatal clinics and labour words of Ain Shams University Maternity hospital.

Inclusion criteria: We had three groups of pregnant women in the third trimester. The first group is normotensive women. The second group is pregnant women in the third trimester with non-severe preeclampsia (Preeclampsia is defined as sustained Blood pressure ≥ 140/90 in 2 occasions 6 hours apart (not more than 1 week apart) plus Proteinuria ≥ 300mg/24-h urine after 20 weeks of gestation).

The third group is pregnant women in the third trimester of pregnancy with severe preeclampsia (severe preeclampsia is defined as systolic blood pressure more than 160 or diastolic blood pressure more than 110. Also if there is systemic affection as HELLP syndrome).

Exclusion criteria: Pregnant women with history of deep vein thrombosis or known hypercoagulable state for example thrombophilia, pregnant women with chronic hypertension, pregnant women with cardiovascular, autoimmune, renal or hepatic diseases and pregnant women who have diabetes were excluded from the study.

Sample size justification: Sample size was calculated using G* Power versio 3.1.9.2, setting the power (β) at 0.02 and the significance level (α) at 0.02. Data from previous reports [10] indicated that the mean serum thrombomodulin level in control, mild preeclampsia and severe preeclampsia patients was 9.8 ± 4.92, 12.5 ± 6.0 and 21.2 ± 10.84 ng/mL respectively. Calcualtion according to these values produced a minimal total sample size of 117 women. Assuming a drop-out rate of 5%, a total drop-out inflated sample size of 123 women approximately was needed; with 41 women in each study group.

Procedures

All patients were subjected to the following:

Patient's evaluation focusing on detailed history including the onset of the maternal syndrome and detailed clinical examination.

Laboratory investigations included CBC, serum alanine aminotransferase (ALT) and, Aspartate aminotransferase (AST) levels, Serum creatinine, Coagulation profile (prothrombin time [PT], activated partial thromboplastin time [aPTT], and fibrinogen, serum lactate dehydrogenase level (LDH), plasma thrombomodulin (TM) was measured with enzyme Linked Immunosorbent assay (ELISA), Urine: albumin assessment by dipstick, Urinary albumin creatinine ratio (uACr).

Methodology

The subjects consisted of 41 patients with non-severe preeclampsia, 41 normotensive pregnant women in third trimester, and 41pregnant female with sever preeclampsia. Blood samples were collected before any medical intervenion and centrifuged for 20 min at 2,000 rpm. The resulting plasma samples were stored at -70°C until assayed. Preeclampsia defined as a systolic or diastolic blood pressure > 140 or 90 mm Hg, respectively, on two occasions recorded 24 h apart with the presence of proteinuria (>500 mg/day) in a woman who had been normotensive during the first 20 weeks of pregnancy. Plasma TM was assayed by a one-step sandwich enzyme immunoassay using monoclonal antibodies to human TM using kits. This kit is used to assay the Thrombomodulin (TM) in the sample of Human's serum.

Test principle: This kit uses enzyme-linked immune sorbent assay (ELISA) based on the Biotin double antibody sandwich technology to assay the Human Thrombomodulin (TM). Add Thrombomodulin (TM) to the wells, which are pre-coated with Thrombomodulin (TM) monoclonal antibody and then incubate. After that, add anti TM antibodies labeled with biotin to unite with streptavidin-HRP, which forms immune complex. Remove unbound enzymes after incubation and washing. Add substrate A and B. Then the solution turned blue and changed into yellow with the effect of acid.

To eliminate interassay variation, all 123 samples were assayed in the same run. Data were analyzed statistically using paired Student's t test. A level of $p < 0.05$ was accepted as statistically significant.

Statistical analysis: The collected data were revised, coded, tabulated and introduced to a PC using Statistical package for Social Science (SPSS 20.0.1 for windows; SPSS Inc, Chicago, IL, 2001). Quantitative variables are expressed as mean and SD, or Median and Interquartile range (IQR) according to distribution of data. Qualitative variables are expressed as frequencies and percents. Student t test and Mann Whitney test were used to compare a continuous variable between two study groups. Chi square test were used to examine the relationship between Categorical variables. P-value: Level of significance: P>0.05: Non-significant (NS), P<0.05: Significant (S) and P<0.01: Highly significant (HS).

RESULTS

Descriptive analysis of demographic characteristics of pre-eclampsia and control groups are shown in **Tab. 1.** Descriptive analysis of demographic characteristics of mild and severe pre-eclampsia sub-groups are shown in **Tab. 2.** Descriptive analysis of clinic-pathological features of pre-

eclampsia patients and healthy control groups are shown in **Tab. 3.** Descriptive analysis of clinic-pathological features of studied groups are shown in **Tab. 4.** Comparative analysis for serum thrombomodulin protein level between pre-eclampsia patients and healthy control group Mann-Whitney test are shown in **Tab. 5.** Comparative analysis for serum thrombomodulin protein level between mild and severe pre-eclampsia patients group Mann-Whitney test are shown in **Tab. 6.** Prognostic potential of serum thrombomodulin protein level in discrimination between mild and severe cases of pre-eclampsia; ROC curve analysis test are shown in **Tab. 7.**

Receiving operator curve illustrating the prognostic value of serum thrombomodulin in discriminating pre-eclampsia from healthy control group (**Fig. 1.**) and mild from severe pre-eclampsia (**Fig. 2.**).

Tab. 1. Descriptive analysis of demographic characteristics of pre-eclampsia and control groups.

Variables	Statistics	Preeclampsia n=82	Control n-41
Age (years)	Mean ± SD	31.5±5.0	22.7±4.5
	Range	20 - 42	17 - 34
Gestational age (weeks)	Mean ± SD	34.17±3.0	34.2±3.2
	Range	28 - 39	28 - 38
Gravity (number)	Mean ± SD	2.0±1.0	2.2±0.8
	Range	1 - 5	1 - 3
Parity (number)	Median (IQR)	1(2)	1 (2)
	Range	0 - 3	0 - 2
BMI (kg/m$^{2)}$	Mean ± SD	32.0±3.8	21.0±5.0
	Range	24 - 38	18 - 33
SD: standard Deviation; BMI: Body Mass Index, n=number of cases			

Tab. 2. Descriptive analysis of demographic characteristics of mild and severe pre-eclampsia sub-groups.

Variables	Statistics	Mild Preeclampsia N=41	Severe preeclampsia N=41
Age (years)	Mean ± SD	28.4±4.0	34.6±4.0
	Range	20 - 39	22 - 42
Gestational age (weeks)	Mean ± SD	33.3±3.3	36.0±2.6
	Range	28 - 39	28 - 38
Gravity (number)	Mean ± SD	2.0±1.0	1.98±0.9
	Range	1 - 5	1 - 5
Parity (number)	Median (IQR)	1(2)	1 (2)
	Range	0 - 3	0 - 3
BMI (kg/m$^{2)}$	Mean ± SD	31.0±4.0	32±3.4
	Range	24 - 38	24 - 38
SD: Standard Deviation; BMI: Body Mass Index, n=number of cases			

Tab. 3. Descriptive analysis of clinic-pathological features of pre-eclampsia patients and healthy control groups.

Variables	Total	Preeclampsia N=82	Control n-41	Statistics	P value
History of CS					
Negative	75(61)	54(66)	21(28)	U=2.4	0.08 (NS)
Positive	48(39)	28(34)	20(42)		
Number of CS					
One CS	23(48)	15(53)	8(35)	U=5.4	0.001 (NS)
Two CS	21(44)	9(33)	12(57)		
Three CS	4(8)	4(14)	0		
Hypertension					
Negative	49(40)	16(20)	33(67)	U=42.4	0.001 (HS)
Positive	74(60)	66(80)	8(11)		
Blood Pressure					
Normotensive	12(10)	8(10)	4(33)	F=56.0	0.001 (HS)
Hypertensive	66(54)	54(66)	12(18)		
Hypotensive	45(37)	20(24)	25(56)		
BMI (Kg/m^2)					
Healthy (18 – 25)	41(33)	8(10)	33(8)	U=61.5	0.001 (HS)
Obese (>25)	82(67)	74(90)	8(10)		
History of PET					
Negative	85(70)	44(54)	41(48)	U=27.5	0.001 (HS)
Positive	38(30)	38(46)	0		
U: Mann-Whitney test value; F: ANOVA test value; ANOVA: analysis of variances; HS: high significant difference ($p \leq 0.01$); NS: non –significant differences ($p > 0.05$); S: significant difference ($p \leq 0.05$); ǂ: the significance was detected only between normotensive and hypertensive cases when post-Hoc test was conducted					

Tab. 4. Descriptive analysis of clinic-pathological features of studied groups.

Variables	Total	Mild Preeclampsia N=41	Severe preeclampsia N=41	Statistics	P value
History of CS					
Negative	54(66)	27(36)	27(36)	U=0.0	0.6 (NS)
Positive	28(34)	14(29)	14(29)		
Number of CS					
One CS	15(54)	7(30)	8(35)	U=0.18	0.9 (NS)
Two CS	9(32)	5(24)	4(19)		
Three CS	4(14)	2(50)	2(50)		
Hypertension					
Negative	16(20)	16(33)	0	U=19.8	0.001 (HS)
Positive	66(80)	25(34)	41(55)		
Blood Pressure					
Normotensive	8(10)	8(20)	0	F=42.5	0.001 (HS)
Hypertensive	54(66)	13(39)	41(62)		
Hypotensive	20(24)	20(41)	0		
BMI (Kg/m²)					
Healthy (18 – 25)	8(10)	7(17)	1(20)	U=4.9	0.03 (HS)
Obese (>25)	74(90))	34(42)	40(49)		
History of Pre-eclampsia					
Negative	44(54)	27(32)	17(20)	U=4.6	0.02 (HS)
Positive	38(46)	14(37)	24(63)		
Symptoms of Pre-eclampsia					
Negative	9(11)	9(21)	0	U=10	0.001 (HS)
Positive	73(89)	32(40)	41(51)		
Presenting Symptoms					
Neurological	37(51)			F=11.5	0.02 (S)
Oedema	9(12)	15(40)	22(60)		
Gastric	18(25)	5(57)	4(43)		
Antepartum Haemorrhage	6(8)	6(33)	12(67)		
Cardiac manifestations	3(4)	6(100)	0		

U: Mann-Whitney test value; F: ANOVA test value; ANOVA: analysis of variances; HS: high significant difference ($p \leq 0.01$); NS: non –significant differences ($p > 0.05$); S: significant difference ($p \leq 0.05$); ǂ: the significance was detected only between normotensive and hypertensive cases when post-Hoc test was conducted

Tab. 5. Comparative analysis for serum thrombomodulin protein level between pre-eclampsia patients and healthy control group Mann-Whitney test.

Group	Serum thrombomodulin (pg/ml)			
	Median	Range	Statistics	P value
All	674	34 - 3414		
Pre-eclampsia	1244	314 - 3414	U=0	0.001 (HS)
Control	174	34 - 276		

U: Mann-Whitney test value "U = 0 " means that all your values in one sample are greater compared to all the values in the other sample. " p value =0.000 " means p Value<0.0001

DISCUSSION

Preeclampsia is a multi-systemic disorder of unknown cause. Endothelial cell damage has recently been suggested to underlie the pathologic change in preeclampsia pregnancy. Thrombomodulin an endothelial cell surface glycoprotein act as a co-factor for thrombin catalysed activation of protein C. activated protein C inhibits coagulation by inactivation the coagulation factor Va and VIIIa [1].

In this study, blood samples were collected before any medical intervenion and centrifuged for 20 min at 2,000 rpm. The resulting plasma samples were stored at -70°C until assayed. Plasma TM was assayed by a one-step sandwich enzyme immunoassay using monoclonal antibodies to human TM using kits.

Regarding clinic-pathological features of pre-eclampsia patients and healthy control groups, our study found that there was high significant difference ($p \leq 0.01$) between hypertensive and normal patients regarding (hypertension, obesity and history of PET).Our study found that there was high significant difference ($p \leq 0.01$) between pre-eclampsia patients and healthy control group regarding serum thrombomodulin protein level and serum thrombomodulin protein increases significantly with mild and severe preeclampsia and HELLP syndrome and considered a good marker for evaluation of hypertensive patients with pregnancy.

Herbst et al., [11] study assessed the relationships between thrombomodulin and the occurrance and persistence of preeclampsia agreed with our results and found that thrombomodulin level was higher in PET at initial evaluation (60.8 vs 41.5), delivery (64.3 *vs* 38.0), 24 hrPP (50.6 *vs* 27.5) and discharge (45.0 *vs* 26.9), $p<0.02$

Tab. 6. Comparative analysis for serum thrombomodulin protein level between mild and severe pre-eclampsia patients group Mann-Whitney test.

Group	Serum thrombomodulin (pg/ml)			
	median	range	statistics	P value
Pre-eclampsia				
Mild	674	314 – 1154	U=0	0.0001 (HS)
Severe	2294	1334 - 3414		
History of CS				
Negative	1484	522 - 3374		
Positive	-	-	-	-
Number of CS				
One CS	2054	522 – 3014	F=0.02	0.98 (NS)
Two CS	914	634 – 3374		
Three CS	1514	874 - 2774		
Symptoms				
Negative	614	314- 1154	U=0	0.001 (HS)
Positive	2054	355 - 3414		
Presenting Symptoms				
Neurological	2074	434 – 3414	F=2.9	0.027 (S)
Lower limb oedema	914	374 – 3374		
Gastric manifestations	2154	522 – 2774		
Anti-partum Haemorrhage	699	355 – 815		
Cardiac manifestations	2574	2294 - 2754		
Hypertension				
Negative	664	314 – 934	U=193	0.001 (HS)
Positive	2154	374 - 3414		
Blood pressure status				
Normotensive	554	314 – 874	F=29.9	0.001ǂ (HS)
Hypertensive	2194	374 – 3414		
Hypotensive	704	522 - 954		
Body mass index (Kg/m²)				
Healthy (18 – 25)	784	434 – 2334	U=182	0.07 (NS)
Obese (>25)	1754	314 - 3414		
History of Pre-eclampsia				
Negative	824	314 – 3414	U=570	0.01 (HS)
Positive	2174	434 - 3254		

U: Mann-Whitney test value; F: ANOVA test value; ANOVA: analysis of variances; HS: high significant difference ($p \leq 0.01$); NS: non –significant differences ($p > 0.05$); S: significant difference ($p \leq 0.05$); ǂ: the significance was detected only between normotensive and hypertensive cases when post-Hoc test was conducted

Tab. 7. Prognostic potential of serum thrombomodulin protein level in discrimination between mild and severe cases of pre-eclampsia; ROC curve analysis test.

Groups	Cut-off	AUC	Asymptotic 95% Confidence Interval Lower bound – Upper bound	Biomarker sensitivity (%)	Biomarker specificity (%)
Pre-eclampsia/ Control	904	0.855	0.76 – 0.95	72%	80%
Mild pre-eclampsia/ Severe	1054	0.97	0.94 – 1.00	70%	95%

each. Thrombomodulin at 24 hrPP and at discharge was higher in PET vs. non-pPET. However this study antagonized our results and regression analysis revealed thrombomodulin was not altered by maternal BMI.

Wiwanitkit, [9] study evaluated the correlation between thrombomodulin and severe preeclampsia was in line with our results and found that the overall average thrombomodulin level for the patients and controls was 66.7 + 11.9 ng/mL and 45.7 + 7.3 ng/mL, respectively. The average thrombomodulin level in the patients was significantly higher than in the controls (P <.05).

Alpoim et al., [12] study partially agreed with our study and found that TM plasma concentrations were higher in early sPE women [4782 (209–20565) pg/ml] than in late sPE women [1908 (209–6249) pg/ml] (P=0.05) and disagreed with us as there was no difference was found in TM levels when early sPE and late sPE women were compared with normotensive pregnant women [2103 (299–14063) pg/ml].

Ramireza et al., [13] study which studied the increased tissue factor and thrombomodulin expression and histopathological changes in placentas of pregnancies with preeclampsia agreed with us and found that with respect to the normalized expression of thrombomodulin, for the controls, the thrombomodulin expression level was 0.00029-fold the expression of GAPDH; in contrast, for the cases, the thrombomodulin expression level was 59.57-fold higher than the expression of GAPDH. These results demonstrate that the expression of thrombomodulin

Fig. 1. Receiving operator curve illustrating the prognostic value of serum thrombomodulin in discriminating pre-eclampsia from healthy control group.

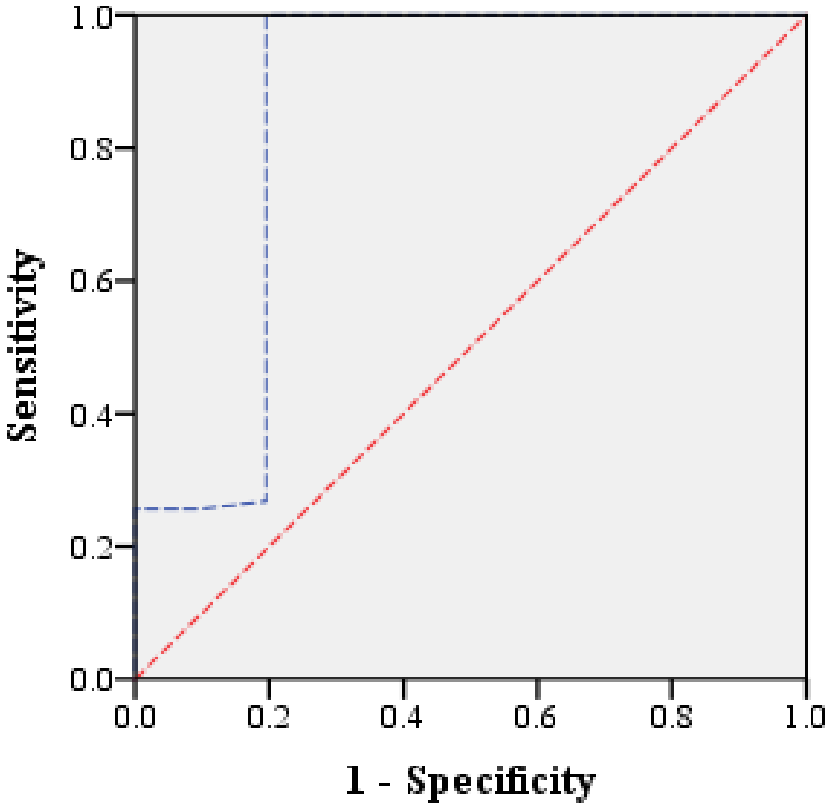
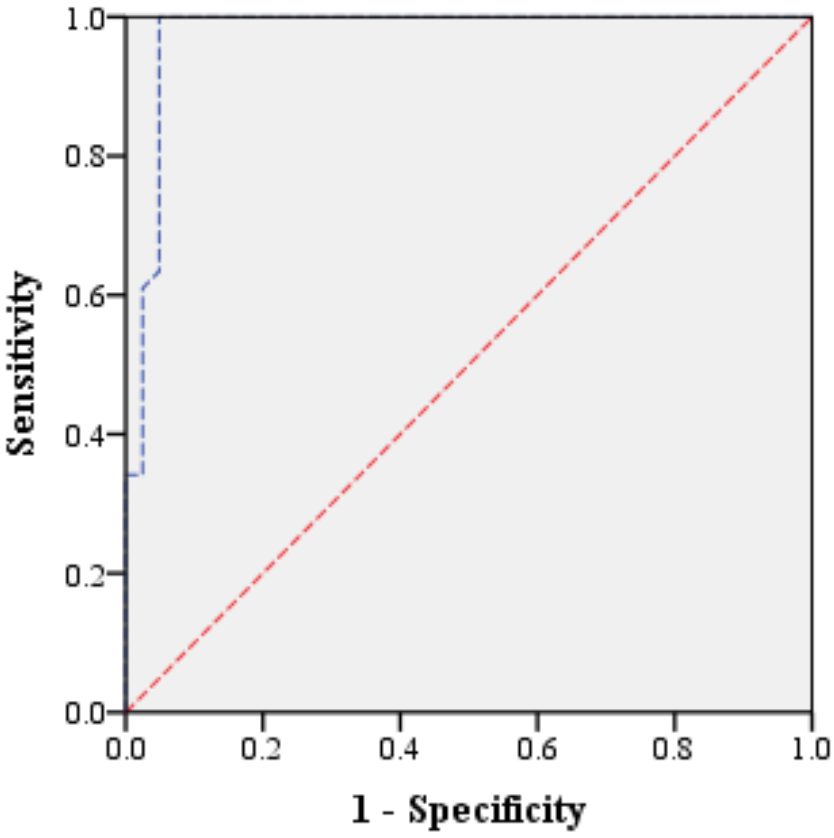


Fig. 2. Receiving operator curve illustrating the prognostic value of serum thrombomodulin in discriminating mild from severe pre-eclampsia.



is 205413-fold greater in cases than in controls. This difference was statistically significant ($p < 0.0001$).

Hsu et al. [7] study evaluated the elevated circulating thrombomodulin in severe preeclampsia partially agreed with us and found that the women with severe preeclampsia but not those with mild preeclampsia, had significantly higher serum thrombomodulin levels than those in the matched control group.

Minakami et al. [14] study studied the increased levels of plasma thrombomodulin in preeclampsia agreed with us and found that plasma thrombomodulin levels were significantly higher in the women with preeclampsia (3.0 ± 1.0 ng/ml; mean ± SD) as compared with all other groups studied, i.e., normal pregnant women (2.0 ± 0.3 ng/ml), normal women in the follicular phase (1.8 ± 0.2 ng/ml) or in the luteal phase (1.8 ± 0.2 ng/ml), or in normal men (1.9 ± 0.4 ng/ml).

Bontis et al. [15] study proved that maternal plasma level of thrombomodulin is increased in mild preeclampsia agreed with us and found that plasma thrombomodulin levels were significantly higher ($P < 0.001$) in pregnant women with preeclampsia than in the normotensive pregnant women and the non-pregnant women.

CONCLUSIONS

Based on the results obtained by this study, serum thrombomodulin protein level is considered a good marker for evaluation of hypertensive patients with pregnancy and can be a suitable tool for prediction of preeclampsia.

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