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Increased thrombomodulin level in hypertensive disorders of pregnancy

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Abstract:

BACKGROUND: Endothelial dysfunction is a likely pathogenic mechanism in hypertensive disorders of pregnancy leading to a hypercoagulable state.

OBJECTIVE: The present study aims to measure thrombomodulin (TM) in patients with preeclampsia (PE) and gestational hypertension (GH) and compare them with healthy pregnant control and its relation to disease severity and associated hematological parameters.

MATERIALS AND METHODS: This cross-sectional study was done for 80 participants, 30 preeclamptic, 30 GH patients, and 20 healthy age-matched pregnant from all TM assays were done in by an enzyme-linked immunosorbent assay. Other hematological parameters including complete blood count, prothrombin time, and activated partial thromboplastin time where assessed in these patients.

RESULTS: TM level was significantly higher in patients with PE when compared to both women with GH and normal pregnant women ($P = 0.009$) and ($P < 0.001$), respectively. Likewise, TM level was significantly higher in patients with GH when compared to healthy pregnant controls ($P = 0.034$). Plasma TM level was found to be 77% sensitive and 75% specific for the diagnosis of PE (the area under the curve was 0.835) at a 95% confidence interval.

CONCLUSION: TM is significantly elevated in pregnant women with PE and GH and is associated with the severity of the disease.

Keywords:

Gestational hypertension, preeclampsia, thrombomodulin

Introduction

Hypertensive disorders in pregnancy, including gestational hypertension (GH) and preeclampsia (PE), accounting for approximately 7%–10% of all pregnancies in developing countries, are the major causes for maternal and perinatal morbidity and mortality.[1] The occurrence of new arterial hypertension in pregnancy with the absence of proteinuria has been termed as GH due to the point that it occurs during gestation.[2] The etiology of PE is not fully understood though it has been linked with a widespread maternal endothelial dysfunction originating from an insufficient cytotrophoblast invasion and then hypoxic placenta.[3] Thrombomodulin (TM) is an endothelial cell surface glycoprotein that is widely distributed on vascular endothelial cells. It acts as a receptor for thrombin binding that mediates activation of protein C, thus inhibit thrombin activity.[4] It is an important regulator of thrombotic and inflammatory processes. Soluble TM fragments have been detected in the blood and urine of healthy individuals and increased particularly in endothelial injury.[5] The present study aims to evaluate the level of TM among pregnant females with GH and PE and to determine whether there is a relationship between the increased level of TM and the severity of both diseases.

Patients, Materials, and Methods

A total of 80 women were included in this case–control study that was performed at

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Al-Imamein Al-Kadhimein Medical City and Baghdad Teaching Hospital/Baghdad, during the period from the 1st of January till the end of June 2020. Those patients comprised 30 pregnant women with PE, who were diagnosed according to the diagnostic criteria of PE by a consultant gynecologist, 30 pregnant females with GH who were diagnosed with blood pressure ≥140/90, and 20 normotensive healthy pregnant females in their third trimester of pregnancy to be served as a control group. This study was approved by review ethical committee of Al-Nahrain university college of medicine. All patients and controlled subject were signed written informed consent prior to enrollment in the study.

Data that includes name, age, past obstetric history (gravidity, parity, previous abortion, previous history of PE, and other complications) past medical, surgical, and drug history, along with blood pressure and urine analysis were collected by direct interview or from the hospital records. Exclusion was done for: those patients who take anticoagulants, those with liver, renal, and vascular disease, patients with current thrombosis or Disseminated intravascular coagulation (DIC), within the last 3–6 months, patients with COVID-19, or any infection during the active illness of the disease.

Four ml of blood was obtained from all participants: 2 mL of blood was added to the K3-ethylenediaminetetraacetic acid tube for complete blood count (CBC) and 2 mL was added to the sodium citrate tube to obtain plasma by centrifugation for immediate assay of prothrombin time (PT) and activated partial thromboplastin time (PTT) in the hematology laboratory at Al-Imamein Al-Kadhimein Medical City, part of citrated plasma was stored (below –40°C) for TM assay. Blood samples were checked out for CBC by Sysmex XN-1000 Automated Hematology Analyzer (Sysmex Corporation, Japan). PT was performed using The STA®-NeoPTimal kit from (Diagnostica Stago, France), and activated partial thromboplastin time (aPTT) was performed using The STA®-Cephascreen® kit (Diagnostica Stago, France) according to the manufacturer instructions. Platelet-poor plasma was prepared by centrifuging of citrated blood of both the patients and control for 15 min at 2000 g. Both PT and aPTT were carried out by fully automated STA Compact Max2 (Diagnostica Stago, France).

TM estimation was done by enzyme-linked immunosorbent assay using commercially available Human TM/BDCA-3 Immunoassay kit, R and D Quantikine, USA.

For statistical analysis, data were made using SPSS software (version 20.0, IBM, Armonk, New York, USA). The numerical data were represented as mean ± standard deviation and nominal data were represented as numbers and percentages. Data between patients and controls were analyzed by the Student's *t*-test and ANOVA test. Correlations were done by Pearson's method. P <0.05 was considered statistically significant.

Results

The mean age of PE patients was 30.03 ± 6.92 years which did not differ significantly from that of women with GH (mean: 27.53 ± 4.72 years). In general, primigravida and nulliparous patients were more common among women with PE than those with GH; however, the differences were insignificant. The majority of patients with PE (83.33%) and those with GH (93.3%) did not experience PE before. Patients with mild PE comprised 17/30 (56.67%) of the studied PE patients, while those with severe PE comprised 13/30 (43.33%) of the total PE patients. Regarding blood pressure, preeclamptic patients showed higher systolic blood pressure (SBP) and diastolic blood pressure (DBP) (158.43 ± 18.9 mmHg and 96.17 ± 11.92 mmHg, respectively) than women with GH (139.4 ± 8.84 mmHg and 85.07 ± 3.63 mmHg, respectively) with highly significant differences (P < 0.001) as shown in Table 1.

Anemia was found in 4/30 (13.3%) of preeclamptic patients and in 8/30 (26.7%) of patients with GH.

Table 1: Demographic and reproductive characteristics of the study population

Variables	PE (*n*=30), *n* (%)	GH (*n*=30), *n* (%)	*P*
Age (years)			
Mean±SD	30.03±6.92	27.53±4.72	0.108
Range	17-44	16-38	
Parity			
Nulliparous	11 (36.7)	8 (26.7)	0.405
Multiparous	19 (63.3)	22 (73.3)	
Gravida			
Primigravida	8 (26.7)	6 (20)	0.542
Multigravida	22 (73.3)	24 (80)	
Previous abortion			
No	21 (70)	24 (80)	0.371
Yes	9 (30)	6 (20)	
Previous PE			
No	25 (83.33)	28 (93.3)	0.228
Yes	5 (16.67)	2 (6.7)	
SBP (mmHg)			
Mean±SD	158.43±18.9	139.4±8.84	<0.001
Range	140-200	125-155	
DBP (mmHg)			
Mean±SD	96.17±11.92	85.07±3.63	<0.001
Range	85-120	80-90	
Severity			
Mild	17 (56.67)		
Severe	13 (43.33)		

SD=Standard deviation, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, PE=Preeclampsia, GH=Gestational hypertension

Regarding platelets count the proportion of patients with thrombocytopenia in PE was 7/30 (23.3%), while in GH, it was only 1 out of 30 (3.3%) [Table 2]. Normal ranges are shown in Appendix 1 later on.

There were no significant differences between the three groups regarding mean values of hemoglobin (Hb), white cell count (WBC), absolute neutrophil count (ANC), platelet count, PT, and PTT. Mean platelet volume (MPV) was significantly higher among PE patients but not in the GH group when compared with the control group as shown in [Table 3].

The mean plasma level of TM in PE patients was significantly higher than that of women with GH and healthy pregnant controls. Furthermore, the statistical analysis showed a significant difference between women with GH and healthy pregnant control as shown in Figure 1.

Table 2: Frequency of hematological parameters of the studied participants

Parameter	PE (*n*=30), *n* (%)	GH (*n*=30), *n* (%)	Control (*n*=20), *n* (%)
Hb (g/dL)			
<10.6	4 (13.3)	8 (26.7)	5 (25)
10.6-15	25 (83.3)	22 (73.3)	15 (75)
>15	1 (3.3)		
T.WBC (× 10^9/L)			
<4		1 (3.3)	
4-10.6	20 (66.7)	22 (73.3)	14 (70)
>10.6	10 (33.3)	7 (23.3)	6 (30)
Platelets (× 10^9/L)			
<150	7 (23.3)	1 (3.3)	
150-400	23 (76.7)	29 (96.7)	20 (100)
>400			

PE=Preeclampsia, GH=Gestational hypertension, WBC=White blood cell, Hb=Hemoglobin, T.WBC=Total white blood cell

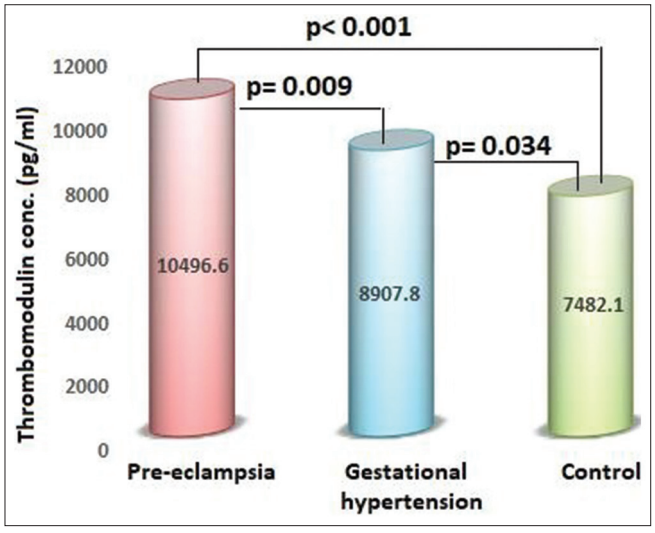

Figure 1: Mean plasma level of TM in PE patients, women with GH and healthy pregnant women. TM = Thrombomodulin, PE = Preeclampsia, GH = Gestational hypertension

In the context of discrimination between PE and controls, area under the curve (AUC) was 0.835 (95% confidence interval = 0.724–0.946), $P < 0.001$. The sensitivity and specificity of the test at the cutoff value of TM = 8593.9 pg/ml were 77% and 75%, respectively, as shown in Figure 2.

There was a positive correlation between TM level and both SBP and DBP as displayed in [Table 4].

In preeclamptic patients, the mean plasma level of TM was found to be higher in nulliparous women than in multiparous with a significant difference ($P = 0.007$). Furthermore, in preeclamptic patients, those with a history of previous abortion had higher mean plasma TM levels than those without a history of abortion with $P = 0.018$. Regarding severity, severe cases of PE demonstrated a higher level of mean TM than mild cases with a significant difference ($P = 0.002$) [Table 5].

Discussion

While there is evidence supporting the dysfunction of the vascular endothelium in PE, there has been little work on the role of the vascular endothelium in GH. There are many endothelial markers, but in our study, we chose to evaluate TM in both GH and PE.

Hb, WBC, ANC, platelet count, PT, and PTT were done to all patients included in this study and their mean values showed no significant differences from the control group. Anemia in the studied cases was found to be a less

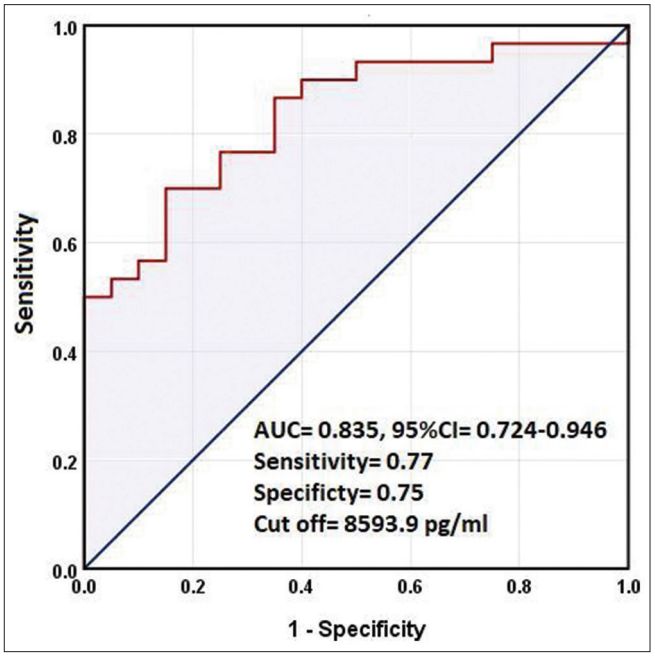

Figure 2: ROC curve for TM in the context of discrimination between PE and healthy controls. ROC = Receiver operating characteristic, TM = Thrombomodulin, PE = Preeclampsia, AUC = Area under the curve, CI = Confidence interval

Table 3: Comparison of hematological parameters in control and two patients groups

Variables	Control (*n*=20)	Group			
		GH (*n*=30)	*P*	PE (*n*=30)	*P*
Hb (g/dL)					
Mean±SD	10.95±1.02	11.18±0.75	0.758	11.66±1.5	0.084
Range	9.00-12.80	9.80-12.30		8.60-15.1	
WBC (× 10^9/L)					
Mean±SD	9.44±2.1	10.05±2.27	0.585	10.03±1.95	0.606
Range	5.90-13.2	4.80-14		5.38-15.5	
ANC (× 10^9/L)					
Mean±SD	5.98±2.29	6.43±2.95	0.845	6.28±2.77	0.933
Range	2.4-10.2	2.1±11.4		1.70-13.52	
Platelets (× 10^9/L)					
Mean±SD	237.65±50.39	220.7±49.1	0.626	209.17±81.24	0.271
Range	156-312	112-322		68-326	
MPV (fL)					
Mean±SD	8.44±1.78	9.19±1.6	0.277	10.17±1.72	0.002*
Range	4.9-11.5	6.4-12.8		7.1-14.2	
PT (s)					
Mean±SD	12.97±0.66	12.92±0.9	0.985	12.37±0.99	0.058
Range	11.2-13.8	11.5-14.5		10.2-14.7	
PTT (s)					
Mean±SD	31.88±2.73	32.35±1.8	0.749	33.04±2.31	0.178
Range	27.3-35.7	27.5-35.4		29.5-38.8	

SD=Standard deviation, PE=Preeclampsia, GH=Gestational hypertension, Hb=Hemoglobin, WBC=White blood cell, PT=Prothrombin time, PTT=Partial thromboplastin time, MPV=Mean platelet volume, ANC=Absolute neutrophil count, (*) Significant at $P \leq 0.05$

Table 4: Pearson's correlation between thrombomodulin and other variables in preeclampsia patients and women with gestational hypertension

Variable	PE		GH	
	r	*P*	*r*	*P*
Age	0.102	0.592	−0.267	0.153
Hb	0.215	0.253	0.163	0.391
WBC	−0.072	0.704	−0.098	0.607
ANC	−0.127	0.505	0.010	0.956
Platelets	−0.179	0.343	0.187	0.322
MPV	0.284	0.128	0.229	0.224
SBP	0.715	<0.001	0.705	<0.001
DBP	0.540	0.002	0.647	<0.001
PT	0.150	0.429	0.159	0.403
PTT	0.100	0.598	−0.296	0.112
Proteinuria	0.279	0.135		

Hb=Hemoglobin, WBC=White blood cell, PT=Prothrombin time, PTT=Partial thromboplastin time, MPV=Mean platelet volume, ANC=Absolute neutrophil count, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, PE=Preeclampsia, GH=Gestational hypertension

frequent finding in PE (13.3%) compared to control (25%) and GH (26.7%) groups. This is most appropriate with the consensus that PE is characterized by endothelial activation and plasma leakage into interstitial tissues to result in pathological edema and hemoconcentration.[6]

Thrombocytopenia may occasionally occur before other manifestations of PE, and thus PE must be considered in the differential diagnosis of isolated thrombocytopenia developing in the third trimester.[7] In the current study, low platelet count was seen in 23.3% of the studied preeclamptic patients and in 3.3% of cases with GH. However, the mean platelet count showed no significant difference between the three groups. While the latter was insignificant in the preeclamptic group in comparison to normotensive pregnant women, other parameters, namely MPV showed a significant difference between the two groups. MPV reflects the average size of platelets in circulation. It is considered a useful surrogate marker of platelet activation or reactivity.[8] In this study, MPV showed a significant increase in PE than in normotensive pregnant women, this strengthened the hypothesis that according to the pathophysiology of PE, endothelial activation leads to increased platelet aggregation which in turn leads to a decrease in the platelet count and accelerated production of new platelets in the circulation. This was similar to those of other studies[9-11] but disagreed with AlSheeha *et al*.[12] and Altınbas *et al*.[13] who observed no significant difference. The utility of MPV in predicting PE has been shown in several studies.[14-17] Thus, it was suggested that the MPV can be used as a valuable marker in the diagnosis and prediction of PE as well as in the prognosis of the disease. However, in this study, for patients with GH, MPV was not significantly increased than in normotensive pregnant women. This result was consistent with that made by Valera *et al*.[18] while it was demonstrated to be increased in other studies done by Baser *et al*.[19] and by Akhila *et al*.[20]

The main parameter that was aimed to be assessed in this study is TM. In the current study, the mean TM

Table 5: Association of thrombomodulin concentration with reproductive and clinical characteristics in preeclampsia patients and women with gestational hypertension (*n*=30)

Variables	PE	GH
Gravida		
Primigravida	10794.7±3991.7	8408.8±1116.3
Multigravida	10388.3±2558.8	9032.6±2183.5
P	0.744	0.507
Parity		
Nulliparous	12312±2890.2	9065.4±1891.5
Multiparous	9445.7±2463.4	8850.5±2098.1
P	0.007	0.801
Previous abortion		
No	9812.1±2267.8	8866±2006.3
Yes	12745.9±3887	9075.1±2234.6
P	0.018	0.825
Previous PE		
No	10521.7±3089.6	
Yes	10371.3±22880.9	
P	0.919	
Severity		
Mild	9130±1955.9	
Severe	12283.7±3102.6	
P	0.002	

PE=Preeclampsia, GH=Gestational hypertension

level in preeclamptic patients was far significantly higher than that of healthy pregnant females. TM is released into circulation only after damage to the endothelial cells.[21] Such damage is supposed to be involved in the development of PE and this in no doubt confirms the findings of the present study. This result was similar to Prochazka *et al*. and Saposnik *et al*. studies which showed that TM level was increased in PE than in normotensive pregnant females,[22,23] while this was not in line with Pottecher *et al*.[24] and Dusse *et al*.[25] studies which showed no statistically significant difference between those two groups. Moreover, in the present study, TM higher plasma levels were found in GH compared to normotensive pregnant women. This might indicate that vascular endothelial abnormalities are recognized to be a dominant process in GH, as also described in Nadar *et al*. study.[26] On the other hand, the mean TM was significantly higher in women with PE than in women with GH. This data further supports a widespread endothelial dysfunction associated with PE. Hsu *et al*.[27] reported that serum TM level was significantly higher in pregnant women with PE than in those with GH or normal blood pressure, but unlike this study, it was not significantly higher in patients with GH compared to normotensive pregnant women. Concerning the severity of PE, the mean TM level was significantly higher in severe preeclamptic pregnancies than in mild preeclamptic pregnancies, which validated that the plasma TM level is associated with the progression of the disease and that it seems to be a major contributor to the development of end-organ involvement in PE. This result was comparable with that of Dusse *et al*.[28] study.

Regarding gravidity and parity, there were no significant differences between preeclamptic patients and the control group which was similar to studies in Japan and Nigeria.[29,30] However, in the preeclamptic group, those with elevated TM show a significant association with nulliparas and those who had previous abortions, this could explain the epidemiological link between PE and nulliparity.[31]

In both GH and PE, plasma TM was positively correlated with both systolic and DBPs. This showed that the level of TM is linked to the degree of endothelial dysfunction in hypertensive disorders of pregnancy, which could be upstream, in the pathogenesis of endothelial dysfunction, or downstream, as a consequence of endothelial dysfunction. Turner *et al*.[32] observed that the placental expression of TM was lowest in those preeclamptic women with the highest DBP, and Nadar *et al*. revealed that plasma TM was significantly correlated only with SBP.[26] The correlations of TM with Hb, WBC, ANC, platelets count, MPV, PT, and PTT were statistically insignificant ($P > 0.05$). These results were comparable to that reported by Hsu *et al*. study.[27] The current study demonstrated that plasma TM level can distinguish women with PE from healthy pregnant ones, at the third trimester with good sensitivity (77%) and specificity (75%) and with a high AUC that was statistically highly significant (AUC = 0.835, $P < 0.001$).

TM level can distinguish women with PE from healthy pregnant ones, at the third trimester with good sensitivity (77%) and specificity (75%) and with a high AUC that was statistically highly significant (AUC = 0.835, $P < 0.001$). Swellam *et al*.[33] displayed that TM level had receiver operating characteristic and AUC = 0.95, $P < 0.001$ at which sensitivity = 81.3% and specificity = 95.2%. However, in a study conducted by Dusse *et al*.,[28] the AUC was equal to 0.66 which was not statistically significant ($P > 0.05$) to discriminate between PE and normotensive pregnant women.

Conclusion

Plasma TM estimation can reflect the severity of endothelial damage in hypertensive disorders of pregnancy which can be related to blood pressure levels. This marker might be used as a valuable prognostic marker in PE and may contribute for the complications associated with it. MPV is an easy accessible marker and it can be useful in diagnosing PE even in the absence of thrombocytopenia. Besides, plasma TM levels can distinguish women with PE from healthy pregnant ones at the third trimester with good sensitivity and specificity.

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Conflicts of interest

There are no conflicts of interest.

References

1. **Kumar** N, Singh AK, Maini B. Impact of maternal serum uric acid on perinatal outcome in women with hypertensive disorders of pregnancy: A prospective study. Pregnancy Hypertens 2017;10:220-5.
2. Ryan RM, McCarthy FP. Hypertension in pregnancy. Obstet Gynecol Reprod Med 2018;28:141-7.
3. Phipps EA, Thadhani R, Benzing T, Karumanchi SA. Pre-eclampsia: Pathogenesis, novel diagnostics and therapies. Nat Rev Nephrol 2019;15:275-89.
4. Anastasiou G, Gialeraki A, Merkouri E, Politou M, Travlou A. Thrombomodulin as a regulator of the anticoagulant pathway: Implication in the development of thrombosis. Blood Coagul Fibrinolysis 2012;23:1-10.
5. Ito T, Thachil J, Asakura H, Levy JH, Iba T. Thrombomodulin in disseminated intravascular coagulation and other critical conditions – A multi-faceted anticoagulant protein with therapeutic potential. Crit Care 2019;23:280.
6. Dai DM, Cao J, Yang HM, Sun HM, Su Y, Chen YY, *et al.* Hematocrit and plasma albumin levels difference may be a potential biomarker to discriminate preeclampsia and eclampsia in patients with hypertensive disorders of pregnancy. Clin Chim Acta 2017;464:218-22.
7. Chaturvedi S, McCrae KR. Thrombocytopenia in Pregnancy. Inplatelets. United States: Academic press;2019. p. 795-812.
8. Leader A, Pereg D, Lishner M. Are platelet volume indices of clinical use? A multidisciplinary review. Ann Med 2012;44:805-16.
9. Mannaerts D, Heyvaert S, De Cordt C, Macken C, Loos C, Jacquemyn Y. Are neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and/or mean platelet volume (MPV) clinically useful as predictive parameters for preeclampsia? J Matern Fetal Neonatal Med 2019;32:1412-9.
10. Thalor N, Singh K, Pujani M, Chauhan V, Agarwal C, Ahuja R. A correlation between platelet indices and preeclampsia. Hematol Transfus Cell Ther 2019;41:129-33.
11. Monteith C, Egan K, O'Connor H, Maguire P, Kevane B, Szklanna PB, *et al.* Early onset preeclampsia is associated with an elevated mean platelet volume (MPV) and a greater rise in MPV from time of booking compared with pregnant controls: Results of the CAPE study. J Perinat Med 2018;46:1010-5.
12. AlSheeha MA, Alaboudi RS, Alghasham MA, Iqbal J, Adam I. Platelet count and platelet indices in women with preeclampsia. Vasc Health Risk Manag 2016;12:477-80.
13. Altınbas S, Toğrul C, Orhan A, Yücel M, Danısman N. Increased MPV is not a significant predictor for preeclampsia during pregnancy. J Clin Lab Anal 2012;26:403-6.
14. Mayer-Pickel K, Stern C, Eberhard K, Lang U, Obermayer-Pietsch B, Cervar-Zivkovic M. Comparison of mean platelet volume (MPV) and sFlt-1/PlGF ratio as predictive markers for preeclampsia. J Matern Fetal Neonatal Med 2021;34:1407-14.
15. Doğan K, Guraslan H, Senturk MB, Helvacioglu C, İdil S, Ekin M. Can platelet count and platelet indices predict the risk and the prognosis of preeclampsia? Hypertens Pregnancy 2015;34:434-42.
16. Moraes D, Munhoz TP, Pinheiro da Costa BE, Hentschke MR, Sontag F, Silveira Lucas L, *et al.* Immature platelet fraction in hypertensive pregnancy. Platelets 2016;27:333-7.
17. Özdemirci Ş, Başer E, Kasapoğlu T, Karahanoğlu E, Kahyaoglu I, Yalvaç S, *et al.* Predictivity of mean platelet volume in severe preeclamptic women. Hypertens Pregnancy 2016;35:474-82.
18. Valera MC, Parant O, Vayssiere C, Arnal JF, Payrastre B. Physiologic and pathologic changes of platelets in pregnancy. Platelets 2010;21:587-95.
19. Baser E, Salgur F, Bilge M, Ozdemirci S, Esinler D, Unlubilgin E, *et al.* The effect of gestational hypertension on the maternal mean platelet volume. Medicine (Baltimore) 2020;9:90-3.
20. Akhila NR, Jayalakshmi L, Devi K. Study of mean platelet volume in gestational hypertension and normal pregnancy. Int J Biomed Res 2015;6:366-9.
21. Martin FA, Murphy RP, Cummins PM. Thrombomodulin and the vascular endothelium: Insights into functional, regulatory, and therapeutic aspects. Am J Physiol Heart Circ Physiol 2013;304:H1585-97.
22. Prochazka M, Procházková J, Lubušký M, Pilka R, Úlehlová J, Michalec I, *et al.* Markers of endothelial activation in preeclampsia. Clin Lab 2015;61:39-46.
23. Saposnik B, Peynaud-Debayle E, Stepanian A, Baron G, Simansour M, Mandelbrot L, *et al.* Elevated soluble endothelial cell protein C receptor (sEPCR) levels in women with preeclampsia: A marker of endothelial activation/damage? Thromb Res 2012;129:152-7.
24. Pottecher J, Huet O, Degos V, Bonnet MP, Gaussem P, Duranteau J, *et al. In vitro* plasma-induced endothelial oxidative stress and circulating markers of endothelial dysfunction in preeclampsia: An observational study. Hypertens Pregnancy 2009;28:212-23.
25. Dusse LM, Carvalho MG, Getliffe K, Voegeli D, Cooper AJ, Lwaleed BA. Increased circulating thrombomodulin levels in pre-eclampsia. Clin Chim Acta 2008;387:168-71.
26. Nadar SK, Al Yemeni E, Blann AD, Lip GY. Thrombomodulin, von Willebrand factor and E-selectin as plasma markers of endothelial damage/dysfunction and activation in pregnancy induced hypertension. Thromb Res 2004;113:123-8.
27. Hsu CD, Copel JA, Hong SF, Chan DW. Thrombomodulin levels in preeclampsia, gestational hypertension, and chronic hypertension. Obstet Gynecol 1995;86:897-9.
28. Dusse LM, Alpoim PN, Lwaleed BA, de Sousa LP, Carvalho Md, Gomes KB. Is there a link between endothelial dysfunction, coagulation activation and nitric oxide synthesis in preeclampsia? Clin Chim Acta 2013;415:226-9.
29. Shiozaki A, Matsuda Y, Satoh S, Saito S. Impact of fetal sex in pregnancy induced hypertension and preeclampsia in Japan. J Reprod Immunol 2011;89:133-9.
30. Musa J, Mohammed C, Ocheke A, Kahansim M, Pam V, Daru P. Incidence and risk factors for pre-eclampsia in Jos Nigeria. Afr Health Sci 2018;18:584-95.
31. Bdolah Y, Elchalal U, Natanson-Yaron S, Yechiam H, Bdolah-Abram T, Greenfield C, *et al.* Relationship between nulliparity and preeclampsia may be explained by altered circulating soluble fms-like tyrosine kinase 1. Hypertens Pregnancy 2014;33:250-9.
32. Turner RJ, Bloemenkamp KW, Bruijn JA, Baelde HJ. Loss of thrombomodulin in placental dysfunction in preeclampsia. Arterioscler Thromb Vasc Biol 2016;36:728-35.
33. Swellam M, Samy N, Wahab SA, Ibrahim MS. Emerging role of endothelial and inflammatory markers in preeclampsia. Dis Markers 2009;26:127-33.

Appendix 1: Normal ranges of hematological parameters

Parameter	Reference value	References
Hb	Not<10.6 (g/dL)	Dacie and Lewis 2017
T.WBC	4.0-10.6 (× 10^9/L)	Rodak's Hematology 2020
Platelet count	150-450 (× 10^9/L)	Rodak's Hematology 2020
MPV	7.0-12.0 (fL)	Rodak's Hematology 2020

MPV=Mean platelet volume, Hb=Hemoglobin, WBC=White blood cell, T.WBC=Total white blood cell