Evaluation of Plasma D-dimer Level in Preeclampsia at Chittagong Medical College Hospital

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Abstract

Background: Preeclampsia is a prevalent pregnancy complication. It is linked to a hyper coagulable condition that raises the risk of both Disseminated Intravascular Coagulation (DIC) and thromboembolism. Patients with preeclampsia have shown changes in their coagulation indices, specifically in D-dimer levels. These changes have been proposed as a very sensitive indicator for identifying abonormal hyper coagulopathy. The objective of this study was to determine the plasma D-dimer level in preeclampsia compared to normal pregnancies and to observe any variations in relation to the severity of the condition.

Materials and method: This study was done at the Department of Biochemistry and the Department of Obstetrics and Gynaecology at Chittagong Medical College (CMC) and Chittagong Medical College Hospital (CMCH) respectively. It was an observational study that analyzed data from a single point in time. The key factors were examined in this study included age, BMI, gestation period, blood pressure, and urine protein level.

Results: Plasma D-dimer level was higher in severe preeclampsia (1.646 ± 1.120) µg/ml as compared to mild preeclampsia (1.024 ± 0.488) µg/ml and normotensive pregnant (0.611 ± 0.141) µg/ml. The D-dimer was significantly correlated with gestational age. There was a significant mean difference in D-dimer level between preeclampsia and normal pregnancy. D-dimer level of 0.668 µg/ml, the sensitivity is 80% and the specificity is 76% for predicting pre-eclampsia. There was also a significant association of D-dimer with preeclampsia.

Conclusion: Preeclampsia is correlated with elevated D-dimer levels in comparison to pregnancies that are considered normal. Plasma D-dimer levels exhibited a positive correlation with the severity of preeclampsia.

Key words: Blood pressure; D-dimer; DIC; Hypercoagulability; Pregnancy; Preeclampsia; Thromboembolism; Urinary protein.

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Introduction

Preeclampsia (PE) is a multifactorial condition that is defined by systolic blood pressure that is equal to or greater than 140 mm Hg or diastolic blood pressure that is equal to or greater than 90 mm Hg when the patient is in bed rest for a minimum of two occasions, six hours apart, and proteinuria that is equal to or greater than 0.3 g/24 hours, measured after the 20th week of pregnancy. Eclampsia, which is characterized by seizures as a symptom of affection of the cerebral arteries, syndrome HELLP (Hemolysis, increased liver enzyme, low platelets) and disseminated intravascular coagulation are all potential outcomes that might develop following the progression of this condition.[1] Pre-Eclampsia (PE) is a complex obstetric disease that affects around 6-8% of pregnancies worldwide. The significant damage to the endothelial cells in the mother and the resulting inflammatory response that affects several systems and organs during the latter stages of pregnancy may be attributed to abnormal invasion of the placenta and the release of harmful substances from the placenta during the first trimester. The elevated blood pressure observed in preeclampsia is most likely a result of endothelial cell injury or dysregulated vasoconstriction of blood vessels. Fluid retention occurs due to heightened permeability of the endothelial cells, whilst the impairment in blood clotting is a consequence of elevated levels of pro-coagulant microparticles in the circulation.[2] Activation of blood coagulation occurs early in the course of

PE. It usually occurs before any noticeable symptoms appear. An increase in thrombomodulin, soluble fibrin, von Willebrand factor, Thrombin Antithrombin Complex (TAT) D-dimers and Factor VIII has been observed in PE.[3,4] Fetal Growth Restriction (FGR) impaired placental perfusion and malfunction in some maternal organs are all outcomes of Preeclampsia (PE) which is linked to fibrin deposition in microvasculature.[5,6] D-dimer is a byproduct of cross-linked fibrin in the plasma and is commonly employed as a marker to rule out Venous Thromboembolism (VTE).[6] Elevated baseline levels of D-dimer during pregnancy might complicate the interpretation of d-dimer readings when assessing thromboembolism.[7] Several studies showed that patients with PE had higher concentrations of D-dimer.[8] Despite the considerable amount of research conducted on preeclampsia, a screening test has not yet been developed. Given that blood coagulation is initiated at the first phase of the ailments. This study aimed to assess the plasma D-dimer levels in pregnant women with preeclampsia compared to those with normal pregnancies, as well as to examine any variations in these levels based on the severity of the condition.

Materials and methods

This study was conducted in the outpatient departments of Biochemistry and Obstetrics and Gynaecology at Chittagong Medical College Hospital from July 2021 to June 2022. It was a cross-sectional analytical study based in a hospital setting. Following the acquisition of appropriate authorization from the relevant Departments and the ethical review committee, a total of 110 women between the ages of 18 and 42, who were pregnant, were selected for the research using a non-probability purposive sampling approach. A total of 60 individuals were included in the study who had (PE) whereas 50 patients had a normal pregnancy.

Inclusion criteria

- Patient attending CMCH Gynae & Obstetrics Department with signs and symptoms of preeclampsia with age between 18 to 42 years.

Exclusion criteria

- History of diabetes, a systemic or endocrine disorder, chronic infection, chronic renal disease, epilepsy, bleeding disorder, VTE, antiphospholipid syndrome, multiple gestations or any other hepatic disorder.
- Patient using oral contraceptives, and anticoagulant drugs.
- Women with previous recurrent spontaneous abortions, suspected or confirmed DIC.
- Maternal age > 45years, BMI > 40kg/m^2
- Previous history of hypertension.
- Women in active labour.

The cut-off point of normal D-dimer was considered by <0.5 µg/ml

The data was processed and analyzed using Windows version 23.0 of IBM-SPSS, which stands for Statistical Package for the Social Sciences. A statistically significant result will be defined as a p-value less than 0.05. All variables are presented as the mean ± the Standard Error of the Means (SEM) divided by the standard deviation. If the p-value is larger than 0.05, it means that there is no statistically significant difference between the normal distribution and the observed distribution of the variable. In cases where statistical significance needed to be determined, the Pearson correlation test has been utilized.

Results

Table I Comparison of gestational age among normotensive, mild pre-eclampsia and severe pre-eclampsia patients

Gestation (Weeks)	No. of patients	Mean± Std. Deviation	95% CI Lower Bound	Upper Bound	*p-value
Normotensive	50	35.27±4.21	33.41	37.14	0.059
Mild Pre-eclampsia	38	33.32±3.39	32.2	34.43	
Severe pre-eclampsia	22	33.28±3.09	32.4	34.16	

*ANOVA test.

ANOVA test was conducted to compare gestational age among the study subjects. No significant difference (p>0.05) was observed between the three groups. Patients with severe pre-eclampsia had a lower mean gestational age of 33.28±3.09 weeks as compared to patients who were normotensive or had mild pre-eclampsia.

Table II Correlation between gestational age and different parameters of the patients (n=110)

Parameters	Pearson's correlation	*p-value
Systolic Blood pressure and gestational age	0.083	0.387
Diastolic blood pressure and gestational age	0.071	0.459
D-dimer levels and gestational age	0.195	0.042

*Pearson's correlation.

Pearson's correlation was done between gestational age and other parameters. None of the clinical parameters except for plasma D-dimer levels (p=0.042) had a significant positive correlation with gestational age.

Table III Comparison between plasma D-dimer levels among patients with and without pre-eclampsia

Diagnosis	No. of patients	D-dimer level (Mean ± S.D)	95% CI	p- value
Pre-eclampsia	60	1.252 ± 0.829	1.04-1.47	<0.001
Normotensive	50	0.611 ± 0.141	0.57-0.65	

*Student's t-test.

Student's t-test is conducted to compare the levels of D-dimer among patients with and without pre-eclampsia. As observed, the patients with pre-eclampsia have a significantly higher D-dimer level in plasma (p>0.001) as compared to normotensive patients. The mean D-dimer levels among pre-eclampsia patients was 1.252 ± 0.829 with a 95% confidence interval of mean between 1.04 and 1.47. The mean D-dimer levels among normotensive pregnant patients were 0.611 ± 0.141 with a 95% confidence interval of mean between 0.57 and 0.65.

Table IV Comparison of plasma D-dimer levels among pre-eclampsia patients based on the severity

Type of pre-eclampsia	No. of patients	D-dimer level	95% CI	*p- value
Mild	38	1.024 ± 0.488	0.863-1.184	0.004
Severe	22	1.646 ± 1.120	1.150-2.143	

*Student's t-test.

Student's t-test was conducted to compare D-dimer levels among preeclampsia patients based on severity. A highly significant difference (p=0.004) was observed among patients with mild pre-eclampsia and patients with severe pre-eclampsia. Among patients with severe pre-eclampsia, the mean D-dimer level was 1.646 ± 1.120 µg/ml, while in patients with mild to moderate pre-eclampsia, the mean plasma D-dimer level was 1.024 ± 0.488 µg/ml.

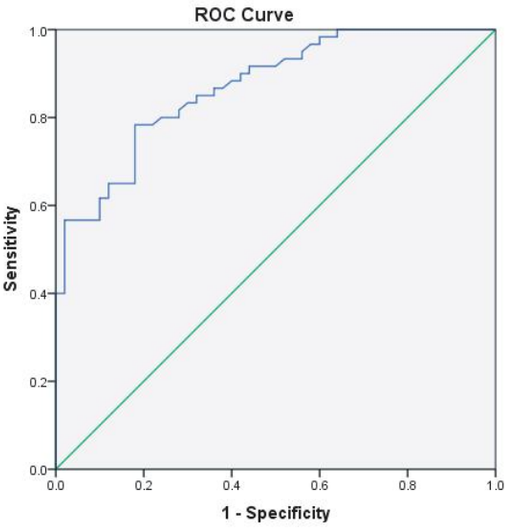

Figure 1 ROC curve for D-dimer levels in predicting pre-eclampsia

To identify a cut-off point in the level of plasma D-dimer to predict pre-eclampsia among pregnant women, an ROC curve was made.The AUC was 0.87 with a 95% CI of 0.807 to 0.933. The p-value was significant at a level below 0.001. At a D-dimer level of 0.668 µg/ml, the sensitivity is 80% and the specificity is 76% for predicting pre-eclampsia.

Table V Association between D-dimer levels and Pre-eclampsia

D-dimer levels	Diagnosis		Total	*p- value
	Pre-eclampsia	Normotensive		
Normal (< 0.5mcg/ml)	0	13 (100%)	13	
		(26%)	(11.8%)	<0.001
Raised (≥0.5mcg/ml)	60 (61.9%)	37 (38.1%)	97	
	(100%)	(74%)	(88.2%)	
Total	60 (54.5%)	50 (45.5%)	110	

*Chi-square test.

Chi-square test was conducted to see the association between D-dimer levels and the patient's diagnosis. As evident from the table, none of the patients with pre-eclampsia had a normal D-dimer level. A significant association was found between raised D-dimer levels (p<0.001).

Discussion

This cross-sectional analytical study aimed to observe and compare the plasma D-dimer level among sixty (60) subjects with preeclampsia and fifty (50) healthy normotensive pregnant women. In addition, other risk factors were assessed to see the association of these factors with D-dimer and preeclampsia. In the present study, preeclampsia patients had a significantly mean higher level of D-dimer (1.252±0.829), ($p<0.001$) compared to normotensive (0.611 ± 0.141) pregnant women (Table III). There was a significant ($p<0.001$) mean D-dimer difference between severe pre-eclampsia, 1.646 ± 1.120 µg/ml, and mild to moderate pre-eclampsia, 1.024 ± 0.488 µg/ml (Table IV).

According to research by Manolov, V. et al. compared to normal pregnancy, preeclampsia is more likely to occur in the third trimester when D-dimer levels are higher.[9] The average D-dimer levels in the control group, preeclamptic patients, and eclamptic patients were 634 ± 228 ng/ml, 1426 ± 430 ng/ml, and 2067 ± 580 ng/ml, respectively, according to the study conducted by Bozkurt M. et al.[10] High D-dimer levels were associated with preeclampsia and eclampsia, respectively, as compared to the control group ($p = 0.034$, $p = 0.020$).[10]

Table II shows that D-dimer levels were positively correlated with gestational age in this study. Kovac et al. shown a direct correlation between gestational age and D-dimer levels.[11] Based on the results, 84% of pregnant women had normal D-dimer levels in the first trimester, 33% in the second, and 1% in the third trimester, when the cutoff was 230 µg/mL (0.23 µg/ml).[11]

Figure 1 depicts that the AUC was 0.87 with a 95% CI of 0.807 to 0.933. The p-value was significant at 0.001. At a D-dimer level of 0.668 µg/ml, the sensitivity is 80% and the specificity is 76% for predicting pre-eclampsia. Like Goldhaber et al. the sensitivity of D-dimer assays was maximal as a function of the duration of preeclampsia.[12] In that study, the sensitivity and specificity of D-dimers were close to 100% in the third trimester of pregnancy.[13] There was also a significant association of elevated D-dimer with preeclampsia (Table V). A significant positive correlation was observed between systolic blood pressure and D-dimer, $p<0.001$ when $r = 0.459$. The correlation between diastolic blood pressure and D-dimer levels was significant at $p=0.01$ when $r(58) = 0.33$.

Consistent with the research by Z Tacoosian et al. the D-dimer levels of preeclamptic women were significantly higher than those of healthy controls.[14] Kucukgoz Gulec U et al. also found comparable results, with substantially higher D-Dimer levels in the study group compared to the control group and in patients with severe pre-eclampsia compared to moderate pre-eclampsia.[15]

Ren H; et al. found that along with other coagulation profiles D-dimer level was significantly higher in severe preeclampsia patients.[16] The risk of disseminated intravascular coagulation is significantly increased during pregnancy, and there was also a natural increase in D-dimer levels during this period. Many researchers have concluded that a high cut-off level is necessary to screen only true positives when using D-Dimeras, an indicator of disseminated intravascular coagulation. This is particularly true in resource-constrained settings where the tool is fast and non-invasive.

Limitations

Due to the limited sample size and the use of a purposeful sampling approach, the results of the study can not provide the actual sensitivity and specificity. The cross-sectional study does not indicate any causal relationships between plasma D-dimer levels with preeclampsia. To learn how plasma D-dimer levels fluctuate in relation to preeclampsia severity and how it affects the condition, further research is needed.

Conclusion

It can be concluded that plasma D-dimer level measurement can be considered as an early, economical and rapid procedure for assessment of the severity of preeclampsia along with other investigations. Increased levels may also act as a future risk of developing VTE and DIC in preeclampsia. Clinically, plasma D-dimer measurement can be a useful screening test for the early identification of preeclampsia and eclampsia.

Recommendations

- It might be possible to draw broader conclusions about the Bangladeshi population if the sample size is much larger.
- For better data, a cohort study is the way to go.
- It is important to pay attention to plasma D-dimer levels and regularly test for it in order to reduce the risk of complications from preeclampsia.
- Early identification of preeclampsia, frequent ANC and healthy lifestyle choices should all be goals of community-based initiatives.

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Contribution of Authors

SSU-Conception, design, acquisition of data, drafting and final approval.
NT-Design, critical revision & final approval.
MHI-Design, critical revision & final approval.
SD-Interpretation of data, statistical analysis, drafting & final approval.
SS-Data analysis, critical revision & final approval.
HS-Acquisition of data, interpretation of data, drafting & final approval.
PG-Interpretation of data, critical revision & final approval.

Disclosure

All the authors declared no conflict of interest.

References

1. ACOG Committee on Obstetric Practice. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. American College of Obstetricians and Gynecologists. International Journal of Gynaecology and Obstetrics: The official organ of the International Federation of Gynaecology and Obstetrics. 2002;77(1):67-75.

2. Al-Jameil N, Aziz Khan F, Fareed Khan M, Tabassum H. A brief overview of preeclampsia. J Clin Med Res. 2014;6:1–7.

3. Dusse LM, Rios DRA, Pinheiro MB, Cooper AJ, Lwaleed BA. Pre-eclampsia: The relationship between coagulation, fibrinolysis and inflammation. ClinChimActa. 2011;412(1–2):17–21.

4. Dusse LM, Carvalho MG, Getliffe K, Voegeli D, Lwaleed BA, Cooper AJ. Increased circulating thrombomodulin levels in pre-eclampsia. ClinChimActa. 2008;387: 168–171.

5. Xiong Y, Zhou SF, Zhou R, Yang D, Xu ZF, Lou YT, et al. Alternations of maternal and cord plasma hemostasis in preeclampsia before and after delivery. Hypertens Pregnancy. 2011;30:347-358.

6. Kim SJ, Ahn HJ, Park JY, Kim BJ, Hwang KR, Lee TS, et al. The clinical significance of D-dimer concentrations in patients with gestational hypertensive disorders according to the severity. ObstetGynecol Sci. 2017;60(6):542.

7. Kawaguchi S, Yamada T, Takeda M, Nishida R, Yamada T, Morikawa M, et al. Changes in D-dimer levels in pregnant women according to gestational week. Pregnancy Hypertens. 2013;3:172-177.

8. Pinheiro MB, Junqueira DR, Coelho FF, Freitas LG, Carvalho MG, Gomes KB, et al. D-dimer in preeclampsia: Systematic review and meta-analysis. ClinChimActa. 2012;414:166-170.

9. Manolov V, Marinov B, Masseva A, Vasilev V. AkushGinekol (Sofiia). AkushGinekol (Sofiia). 2014;53(2):15–18.

10. Bozkurt M, Yumru AE, Sahin L, Salman S. Troponin I and D-Dimer levels in preeclampsia and eclampsia: a prospective study. ClinExpObstet Gynecol. 2015;42(1):26-31.

11. Kovac, M., Mikovic, Z., Rakicevic, L., Srzentic, S., Mandic, V., Djordjevic, V., et al. The Use of D-Dimer with New Cutoff Can Be Useful in Diagnosis of Venous Thromboembolism in Pregnancy. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2010;148:27-30.

12. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. Lancet. 2012;379(9828):1835–1846.

13. Badibanga MK, Kamba MB, Tozin R, Kitenge CKK, Kakwaka CK, Atuba PM. D-dimer concentrations in preeclampsia and normal pregnancy in Kinshasa. OAlib. 2023;10(09):1–13.

14. Tacoosian Z, Javadi HE, Farzam S, Javadi A. Evaluation of correlation between pre-eclampsia with D-Dimer. The Journal of Qazvin University of Medical Sciences. 2007;11(1):62-66.

15. KucukgozGulec U, TuncayOzgunen F, BarisGuzel A, Buyukkurt S, Seydaoglu G, FerhatUrunsak I, et al. An analysis of C-reactive protein, procalcitonin, and D-dimer in pre-eclamptic patients.Am J ReprodImmunol. 2012;68(4):331-337.

16. Ren H, Liu W, Niu A, Zhao X. Fibrinogen to albumin ratio, a novel serum indicator for evaluating the severity of preeclampsia: A single-centre retrospective study. Medicine (Baltimore). 2023;102(13):e33419.