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Original Article

Plasma D-dimer level in preeclampsia and normal pregnancy

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Abstract:

Preeclampsia is an adverse pregnancy condition of hypertension and proteinuria that appears after 20 weeks of pregnancy. It is associated with generalized vasoconstriction, abnormal blood clotting and fibrin deposition within placental microcirculation. D-dimer has been used as a diagnostic marker of production or degradation of fibrin in vivo. This cross-sectional comparative study aimed to evaluate plasma D-dimer level and its relationship with preeclampsia compared to the normal pregnant women. This study was conducted in the Department of Biochemistry, Sylhet MAG Osmani Medical College on 90 pregnant women – 45 were preeclamptic and 45 were normal pregnant women. The studied groups were matched for mean age (p = 0.292), residence area (p = 0.140), level of education (p = 0.321), occupation (p = 0.156), gestational age (p = 0.191), and number of gravida (p = 0.394). Means of both systolic and diastolic blood pressure were significantly higher in preeclamptic patient's group (p = <0.001) and mean values were above normal. The mean of plasma D-dimer level was found significantly higher (p = <0.001) in pre-eclamptic women (1.15±0.38 µg/ml) compared to the normal pregnant women (0.34±0.24 µg/ml) in this study. Elevated D-dimer level found more in preeclampsia group (95.6%) compared to the normal pregnancy group (26.7%) with an odd ratio of 59.12 (95% CI: 12.37 – 282.53, p = <0.001). The plasma D-dimer level positively correlates with the period of gestation (r = 0.448, p = <0.001), systolic blood pressure (r = 0.723, p = <0.001) and diastolic blood pressure (r = 0.707, p = <0.001) and negatively correlate with total platelet count (r = -0.615, p = <0.001). Based on this study findings it can be concluded that Plasma D-dimer may be used as an important diagnostic tool in pregnancy.

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Introduction:

Hypertensive disorder of pregnancy (HDP) is one of the major causes of maternal and fetal morbidity and mortality during pregnancy.[1]

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Globally HDP complicate approximately 10% of total pregnancies, but its etiologies and pathogenesis are not yet fully understood. It was estimated that globally 50,000-75,000 annual deaths are associated with preeclampsia and its related complications.[2]

Preeclampsia is a disorder characterized by hypertension and proteinuria. It is related to endothelial injury, vasoconstriction and hypercoagulability.[3] Pathogenesis of preeclampsia may involve inadequate placental cytotrophoblastic invasion of uterine arteries and endothelial dysfunction.[4] In preeclampsia due to inadequate placental invasion there is increased production and upregulation of placental anti-angiogenic factors, which result in disruption of

maternal endothelium and causing hypertension, proteinuria and other systemic manifestations of preeclampsia.[5] Endothelial dysfunction activates platelets to express procoagulant activities. The procoagulant cells and molecules initiate and propagate the hypercoagulable and prothrombotic states that result in arterial and venous thrombosis, cardiac failure, renal dysfunction and fetal growth restriction.[6]

In normal pregnancy the hemostatic balance displaced toward hypercoagulability state of blood.[7] The balance between coagulation and anticoagulation is vital for regulation of uteroplacental circulation and organ perfusion.[8] This change probably helps to protect pregnant women from fatal hemorrhage during delivery but it can also contribute to increase the thromboembolic risks during pregnancy and puerperium.[9] As thromboembolism is the leading cause of maternal mortality,[10]laboratory monitoring of hemostasis parameters has been useful for assessing potential progression of preeclampsia from moderate to severe and more catastrophic syndromes of HELLP (a severe form of preeclampsia that presented with hemolysis, elevated liver enzyme and low platelet count).[11]

D-dimer is the smallest fragment of fibrin degradation products (FDPs), a small protein fragment present in blood after a blood clot is degraded by fibrinolysis.[12] It is so named because it contains two crosslinked D fragments of the fibrin protein, D-dimer concentration can be determined by a blood test which help to diagnose thrombosis.[13] The standard cut-off value of plasma D-dimer concentration of 0.5 µg/ml is generally used in the non-pregnant population.[12]Normal pregnancy causes the maternal plasma D-dimer concentration to increase progressively from conception until delivery[14] and reached its peak in the early puerperium.[15]It has been reported that 78% and 99% to 100% of pregnant women presented with higher D-dimer concentration than the standard cut-off value in the second and third trimester respectively.[12] Further increases in plasma D-dimer level observed in pregnancy associated with complications like pre-term labor, preeclampsia and abruption-placenta,[16] pulmonary embolism,[17] venous thrombosis and thromboembolism.[18] As the plasma D-dimer level is increasing with the duration of pregnancy, new cut-off value during pregnancy is necessary.[19]However, several studies showed that patients with preeclampsia had higher concentration of D-dimer than normotensive controls.[11,20,21]

Conventionally, plasma D-dimer level has been used as a marker of in vivo fibrin degradation in patient with hypercoagulable state. Pregnancy also has known as hypercoagulable state. Furthermore, preeclamptic patients usually develop a severe prothrombotic state that potentially resulting in life threatening thrombosis and thromboembolism. Thus, preeclampsia becomes associated with maternal and fetal morbidity and mortality worldwide. Plasma D-dimer level has emerged as a useful diagnostic tool for thrombotic conditions in pregnancy. Its concentration is increasing with the progression of pregnancy. Measurement of plasma D-dimer is relatively simple and non-invasive. This study was designed to assess plasma D-dimer level in preeclampsia compared to normal pregnancy.

Methodology:

This cross-sectional comparative study conducted at the Department of Biochemistry and Department of Obstetrics and Gynecology, Sylhet MAG Osmani Medical College, Sylhet, July 2022 to June 2023. Pregnant women of third trimester and aged from 20 to 40 years enrolled in this study. Selected biochemical parameters of known and newly diagnosed preeclamptic women were compared with apparently healthy pregnant women. Pregnant women with diagnosed diabetes (both new and previously known), essential hypertension, deep vein thrombosis, DIC, sepsis, patients of chronic renal disease, hepatic disease, thyroid disorder, history of Covid-19 infection, taking anticoagulant or antiplatelet drugs, and pregnancy with polyhydramnios or oligohydramnios were excluded in this study. The study protocol was approved by the institutional ethical committee (SOMC/2023/41). Furthermore, informed written consent was taken from every study person.

Demographic data and detailed history of present pregnancy taken from both in-patient and out-patient department, then blood sample collected for further laboratory analyses. Plasma D-dimer level was measured following Chemiluminescence immunoassay (CLIA) method by Snibe Maglumi-800 CLIA Analyzer (China). Random blood glucose, serum ALT, serum AST, serum creatinine level was measured by enzymatic colorimetric method with VITROS-350 Autoanalyzer (UK). Platelet count was measured by Fluorescent cytometric method with Sysmax-XS-800i (Japan). Standard laboratory procedure and protocol for aseptic measure strictly followed during whole laboratory analyses.

Duration of pregnancy including fetal wellbeing and amniotic fluid assessed by ultrasonography prior to collecting blood sample. Preeclampsia defined according to the American College of Obstetricians and Gynecologists (ACOG)[22] where participants were considered as preeclamptic when presented with hypertension (systolic blood pressure was ≥140 mmHg and/or diastolic blood pressure was ≥90 mmHg) and persistent proteinuria (protein excretion at least 0.3g per 24 hours or spot urine protein/creatinine ratio ≥30 mg/mmol or at least 2+ protein by dipstick). During the third trimester, plasma D-dimer of <0.5 µg/ml was considered as normal reference value.

All data were statistically analyzed by using window-based computer software device with Statistical Package for Social Science-25 (SPSS-25). Qualitative data were expressed as frequency and percentage and compared by using Chi-Square (χ^2) test. Quantitative data were expressed as mean ±SD (Standard Deviation) and compared by using unpaired t-test. Regression analysis was done to find out correlation. The *p*-value of <0.05 was considered as statistically significant.

Result:

There was a total of 90 pregnant women enrolled in this study, 45 of them were preeclamptic (Group-A) and 45 were normal pregnant women (Group-B). The studied patients were statistically similar in terms of their mean age (26.58±3.78 years versus 26.16±3.00 years, t = 1.059, *p* = 0.292), living area (χ^2 = 2.846, *p* = 0.140), level of education (χ^2 = 4.682, *p* = 0.321), occupation (χ^2 = 3.722, *p* = 0.156), mean gestational age (36.91±3.25 weeks versus 35.98±3.44 weeks, t = 1.318, *p* = 0.191) and mean gravida (2.18±1.40 versus 1.93±1.30, t = 0.856, *p* = 0.394) respectively (Table-I).

Table-I: Demographic parameters of the study subjects.

Parameters	Preeclamptic (n = 45)	Normal (n = 45)	*p*-value
Mean age ± SD	26.58±3.78	26.16±3.00	0.292
Living area			
Urban area	18 (40.0%)	26 (57.8%)	0.140
Rural area	27 (60.0%)	19 (42.2%)	
Educational status			
No education	5 (11.1%)	9 (20.0%)	0.321
Primary	15 (33.3%)	18 (40.0%)	
Secondary	12 (26.7%)	12 (26.7%)	
Higher-Secondary	11 (24.4%	4 (8.9%)	
Graduation and above	2 (4.4%)	2 (4.4%)	
Occupational status			
House-wife	20 (44.4%)	29 (64.5%)	0.156
Business	16 (35.6%)	11 (24.4%)	
Service	9 (20.0%)	5 (11.1%)	
Mean gestational age (weeks)	36.91±3.25	35.98±3.44	0.191
Mean number of Gravida	2.18±1.40	1.93±1.30	0.394
Distribution of Gravida			0.673
Primigravida	25 (55.6%)	22 (48.9%)	
Multigravida	20 (44.4%)	23 (51.1%)	

Means of the heart rate (96.02±9.68 bpm versus 90.84±8.13 bpm, t = 2.747, p = 0.007), SBP (154.22±20.50 mm of Hg versus 115.78±8.12 mm of Hg, t = 11.695, p = <0.001), and DBP (97.00±10.36 mm of Hg versus 73.33±5.64 mm of Hg, t = 13.462, p = <0.001) were significantly higher in pre-eclampsia group compared with apparently normal pregnancy group in this study. Means of the serum ALT level (32.82±5.28 U/L versus 28.31±6.85 U/L, t = 3.498, p = <0.001), and AST level (28.32±3.47 U/L versus 25.69±4.48 U/L, t = 3.113, p = 0.002) found significantly higher in preeclampsia group compared to the apparently healthy pregnant women. In contrast, RBS level (113.16±10.57 mg/dl versus 118.16±10.44 mg/dl, t = 2.258, p= 0.026) and total platelet

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count (172.07±50.28 x103/µL versus 209.00±14.93 x103/µL, t = 4.724, p = <0.001) found significantly lowered in preeclampsia group compared to the apparently healthy pregnant women. However, mean serum creatinine level (0.80±0.10 mg/dl versus 0.75±0.13 mg/dl, t = 2.029, p = 0.050) found statistically not significant between the study groups (Table-II).

Table-II: Comparison of mean heart rate, blood pressure, and selected biochemical parameters.

Parameters	Preeclamptic (n = 45)	Normal (n = 45)	p-value
Heart rate (bpm)	96.02±9.68	90.84±8.13	0.007*
SBP (mm of Hg)	154.22±20.50	115.78±8.12	<0.001*
DBP (mm of Hg)	97.00±10.36	73.33±5.64	<0.001*
Serum ALT level (U/L)	32.82±5.28	28.31±6.85	<0.001*
Serum AST level (U/L)	28.32±3.47	25.69±4.48	0.002*
Serum Creatinine (mg/dl)	0.80±0.10	0.75±0.13	0.050
RBS (mg/dl)	113.16±10.57	118.16±10.44	0.026*
Platelet count (x 10^3/µL)	172.07±50.28	209.00±14.93	<0.001*

SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, RBS: Random Blood Sugar, * = Significant difference

All the pregnant women with preeclampsia presented either one or combination of typical complaints of dependent part edema, headache and visual disturbance. There were 24 (53.3%), 36 (80.0%) and 36 (80.0%) of patients presented with edema, headache and visual disturbance respectively in this study. In contrast, these complaints were found absent in apparently healthy pregnant women (Figure-1).

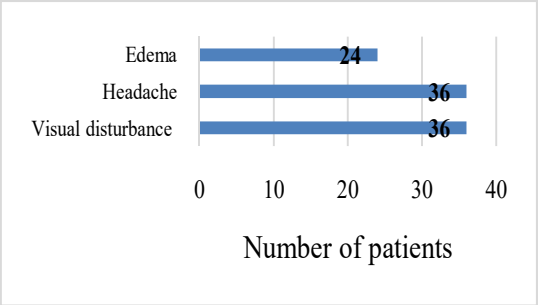

Figure-1: Presenting complaints of preeclampsia.

Mean difference of the D-dimer level found significantly higher (t = 12.128, *p* = <0.001) in preeclampsia group (1.15±0.38 µg/ml) compared to the apparently healthy pregnant women (0.34±0.24 µg/ml) in this study (Figure-2). However, there were more pregnant with preeclampsia group (95.6%) having higher level of serum D-dimer level (<0.5 µg/ml) compared with the apparently healthy pregnant women (26.7%), which found statistically significant (χ^2 = 44.390, *p* = <0.001) in this study (Figure-3). The odds ratio for the D-dimer level for the occurrence of preeclampsia found 59.125 (95% CI: 12.373– 282.538) in this study sample.

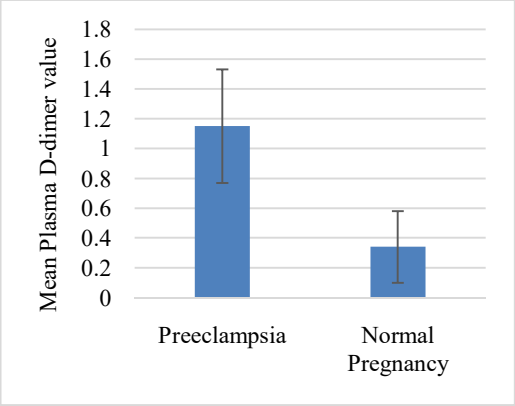

Figure-2: Comparison of D-dimer level between the study groups

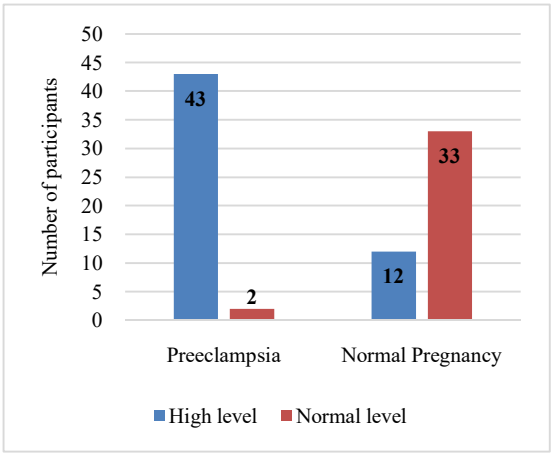

Figure-3: Comparison of study subjects based on their plasma D-dimer status

The simple linear regression analysis used to test to identify the level of prediction of plasma D-dimer level by the period of gestation, SBP, DBP and total platelet count. There was a moderate positive correlation found between the D-dimer level and period of gestation (r = 0.448, r^2 = 0.2005, F = 22.065, *p* = <0.001), between plasma D-dimer level by the SBP (r = 0.723, r^2 = 0.5229, F = 96.439, *p* = <0.001), and between plasma D-dimer level and DBP (r = 0.707, r^2 = 0.5005, F = 88.160, *p* = <0.001) in this study (Figure-4, 5 and 6). However, moderate negative correlation found between plasma D-dimer level and total platelet count (r = -0.615, r^2 = 0.3788, F = 53.654, *p* = <0.001) in this study (Figure-7).

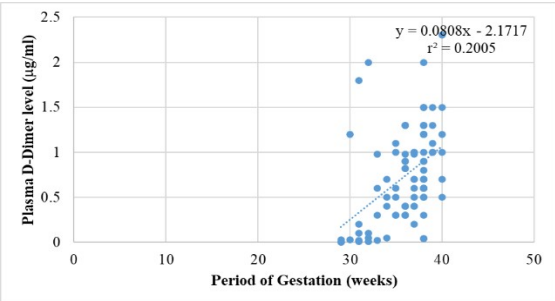

Figure-4: Linear relationship between period of gestation and D-dimer level

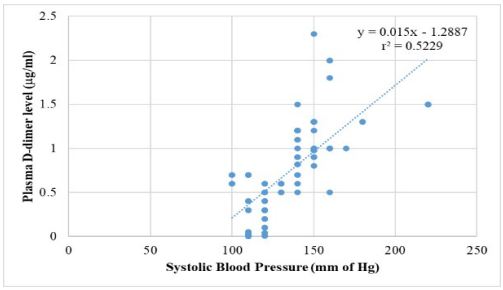

Figure-5: Linear relationship between systolic blood pressure and plasma D-dimer level

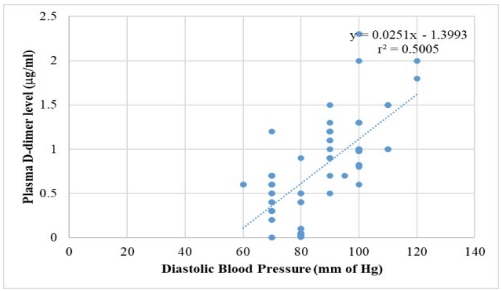

Figure-6: Linear relationship between diastolic blood pressure and plasma D-dimer level

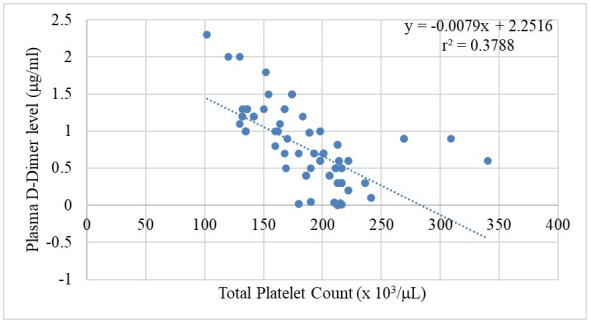

Figure-7: Linear relationship between total platelet count and plasma D-dimer level

Discussion:

Preeclampsia is a multisystem disorder that complicates 14% of pregnancies in our country and constitutes a major source of maternal morbidity and mortality.[23]In preeclampsia there is microvascular fibrin deposition and maternal organ dysfunction occur. D-dimer used as a marker for production/degradation of fibrin in vivo.[8]This study assessed plasma D-dimer level in pre-eclamptic women and normal pregnant women analyzed possible correlation with duration of gestational age, blood pressure and total platelet count.

In this study there were total of 90 pregnant women enrolled, 45 of them were pre-eclamptic women and 45 were normal pregnant women. The comparative groups were matched for their mean age (p = 0.292), age distribution (p = 0.220), living area (p = 0.140), level of education (p = 0.321), and occupation (p = 0.156). The mean period of gestation (p = 0.191), mean gravida (p = 0.394) and distribution based on the gravida status (primi- and multi-gravida, p = 0.673) was also not statistically significant between the study groups. Both systolic (p = <0.001) and diastolic (p = <0.001) blood pressure including mean heart rate (p = 0.007) were found significantly higher in pre-eclampsia group compared to the normal pregnancy group in this study. The means of the SBP and DBP of the pre-eclampsia group found above the normal range. This is justified as elevated blood pressure is an important component of pre-eclampsia that differentiate from the normal pregnancy. Common features of pre-eclampsia such as headache (80% cases), visual disturbance (80% cases) and edema (53.3% cases) presented by the pre-eclamptic patients only. Among the selected biochemical parameters, mean of serum ALT level (p = <0.001) and serum AST level (p = <0.001) observed significantly higher in pre-eclamptic group; random blood sugar (p = 0.026) and total platelet count (p = <0.001) found significantly lower in preeclamptic group in this study. There was no significant difference (p = 0.05) of mean serum creatinine observed in the study. However, none of the mean value nor the absolute value found above the normal reference value among this study subject.

The mean of the plasma D-dimer level in pre-eclamptic patient found 1.15±0.38 µg/ml, which was more than three times higher (p = <0.001) than the normal pregnancy group (0.34±0.24 µg/ml) in this study population. Preeclampsia is associated with the deposition of fibrin in microvasculature. When fibrin polymerization and degradation occur D-dimer appeared in blood. As more fibrin polymerization and degradation occurs during pregnancy, D-dimer concentration is increased. Bozkurt et al. reported more than three-times higher plasma D-dimer level among eclampsia (2.067±0.580 µg/ml, p = 0.020) patients and more than two-times higher in pre-eclampsia (1.423±0.435 µg/ml, p = 0.034) patients compared to the normotensive pregnant women (0.634±0.228 µg/ml) that found in Turkey population.[24] A study in Sudan (1.016±0.158 µg/ml in pre-eclamptic women and 0.168±0.045 µg/ml in normotensive pregnant women, p = <0.001)[25] and another study in Pakistan (plasma D-dimer level in preeclamptic women was 1.02±0.07 µg/ml and the normal pregnant women was 0.18±0.04 µg/ml; p = <0.001)[2] demonstrate significant difference like this study. Further stratification showed significant higher (p = <0.05) plasma D-dimer level in pre-eclamptic female of different age groups and also in females of different period of gestation.[2] However, plasma D-dimer finding of this study found consistent with Shams et al.[2], Bozkurt et al.[24] and Abdelgadir and Gaufri[25].

The frequency of high D-dimer level also found significantly (p = <0.001) higher in preeclampsia (43 of 45, 95.6%) compared to the normal pregnancy (12 of 33, 26.7%) in this study. Odds ratio for the D-dimer level for the occurrence of pre-eclampsia found 59.125 (95% CI: 12.37 – 282.53) in this study sample. Similar to this study, Kim et al.[9], Chowdhury and Mahjabeen[21] and Gulec et al.[26] also reported higher frequency of high plasma D-dimer concentration in pre-eclamptic women compared to normal pregnancy group. However, comparatively low level of odd ratio reported by Gulec et al. (odds ratio 12.3, 95% CI: 4.1 – 36.6)[26] and by Chowdhury and Mahjabeen (odds ratio 11.1, 95% CI: 3.0 – 41.5, p = 0.001)[21] comparted to this study report.

Significant moderate positive correlation of plasma D-dimer level observed with period of gestation (r = 0.448, p = <0.001), systolic blood pressure (r = 0.723, p = <0.001), and diastolic blood pressure (r = 0.707, p = <0.001) in this study. Giavarina et al. reported moderate positive correlation between plasma D-dimer level and period of gestation (r = 0.509, p = <0.001).[10]Baboolall et al. also reported moderate positive correlation between plasma D-dimer and period of gestation (r = 0.648, p = <0.001).[12] More inflammatory response and exaggerated hypercoagulability may play important role for rising D-dimer level in advanced gestation, which was not studied in this study. Similar to

this study, Chowdhury and Mahjabeen also found positive correlation between plasma D-dimer with systolic blood pressure (r = 0.571, p = <0.001) and diastolic blood pressure (r = 0.514, p = <0.05).[21] In preeclampsia hypertension and other systemic manifestation occur as a result of maternal endothelial injury. Which causes disturbance of local anticoagulant properties and activates platelet to express procoagulant activities. There is fibrin deposition occur in microvasculature. When fibrin polymerization and degradation occur relatively stable dimeric fragment (D-D) D-dimer is released into the blood. Thus, rising blood pressure is an important indicator for the thrombotic complications in pregnancy.

The relationship between total platelet counts and D-dimer level was found significantly negative (r = -0.615, p = <0.001) in this study. Significant (p = <0.001) lower mean platelet count was found in pre-eclamptic mother (172.07±50.28 $x10^3/\mu L$) compared to normal pregnant women (209.00±14.93 $x10^3/\mu L$). In preeclampsia platelet activation and consumption of platelet occur during fibrin clot formation and thus platelet count is decreased. D-dimer is a fibrin degradation product. As more fibrin clot formation and degradation occur platelet count will decrease due to platelet consumption. According to the Komarov et al., the elevated level of plasma D-dimer and low platelet count are independent hemostatic predictors of thrombotic events.[27] Heilmann et al. found a negative correlation between plasma D-dimer level and total platelet count (r = -0.578, p = 0.002).[11]

Conclusion:

This study revealed significantly higher level of plasma D-dimer among preeclamptic women. Further analyses showed positive correlation of plasma D-dimer with gestational age and blood pressure, and negatively correlate with total platelet count. From this study, it can be stated that D-dimer may be used as an important diagnostic tool to identify the risk of thrombotic complications in pregnancy.

Limitations:

1. Since it involves one single institution, it may not represent the general population.
2. Sample size of this study was comparatively small to draw conclusion for general population.

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