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Original Article

D-Dimers and Fibrinogen in Third Trimester of Normal Pregnancy and Pregnancy Complicated by Gestational Hypertension or Preeclampsia

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ABSTRACT

Introduction: D-Dimers are very useful for screening thrombotic events as they have high sensitivity because of the high negative predictive value for venous thromboembolism but this increase confounds its use to predict venous thromboembolic events in symptomatic pregnant patients.

Objectives: To determine mean levels of D dimers and fibrinogen among pregnant patients in the third trimester and to compare them in normal pregnant women versus pregnant women with gestational hypertension or pre-eclampsia.

Material and Methods: This descriptive cross-sectional study was carried out in the Department of Hematology, Holy Family Hospital, Rawalpindi from April 2018 to 30th September 2018.A total of 100 pregnant women; 50 pre-eclamptic and 50 normotensives, 15 to 49 years of age were included. Patients with a family or personal history of thromboembolic disease, varicose veins, any type of malignancy, CLD, and with current infection or fever of >38 °C were excluded. Blood sample from each patient was obtained under aseptic measures by using a 3cc BD syringe. D-dimer concentration was measured on fresh plasma within 4 hours of blood collection, in the D dimer latex kit. The fibrinogen concentration was measured using Clauss fibrinogen assays.

Results: In this study, mean levels of D dimers and fibrinogen among pregnant patients in the third trimester were 240.0 ± 112.82 ng/ml and 281.65 ± 51.85 mg/dl. In this study, mean D-dimers during normal pregnancy were 220.0±60.61 ng/ml and in PIH or preeclamptic patients were 260.0±145.69 ng/ml with a p-value of 0.076. Mean fibrinogen levels during normal pregnancy were 280.0±49.72 mg/dl and in PIH or preeclamptic patients were 283.30±54.34 mg/dl with a p-value of 0.752.

Conclusion: This study concluded that mean levels of D dimers and fibrinogen in pregnant women with gestational hypertension or pre-eclampsia are higher as compared to normotensives women but the difference is not statistically significant.

Keywords: preeclampsia, D dimers, fibrinogen

Introduction

Factor I, commonly known as fibrinogen is a glycoprotein that has a pivotal role in clot formation. This soluble form is converted into fibrin by the action of thrombin during the clot formation process. Factor XIII then cross-links fibrin strands to form a firm clot. D-dimers are formed during the process of fibrinolysis as small protein fragments (FDP).[1]

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One of the states of hypercoagulation is pregnancy.[1] In this state fibrinogen levels increase.[2] Fibrinolysis is also increased to a certain degree to maintain homeostasis. There is a progressive increase of D-dimers in maternal plasma from conception till delivery in normal pregnancy .[3]

High blood pressure developing after the 20th week of gestation is known as gestational hypertension while preeclampsia is a multifactorial process in which there is hypertension and proteinuria after the 20th week of gestation. Path physiology of preeclampsia includes both maternal and fetal factors. Endothelial dysfunction and abnormal placentation during early pregnancy may result in decreased placental blood flow and placental bed ischemia causing the release of

molecules toxic to endothelium into the mother's circulation.[3]These disrupt the mother's endothelial function causing hypertension, edema, and proteinuria. Vascular haem concentration and shifting of intravenous fluids to interstitial spaces decrease perfusion. The exaggerated inflammatory response also occurs in preeclampsia. Activation of coagulation pathways and the resultant formation of microthrombi formation further limit blood supply to organs.[4] However, many clinical studies have shown the linkage between changes in maternal serum level of different minerals during pregnancy and aggravation of hypertension.[5] Pregnant ladies with preeclampsia are at increased risk for various complications such as disseminated intravascular coagulation (DIC), placental abruption, cerebrovascular disease, and maternal death[6].

One study conducted in India showed that mean fibrinogen levels in normal pregnant women were 491.52±81.7 mg/dl and in preeclamptic women were 654.5±131.74 mg/dl.[6] Another study showed that mean D-dimers during normal pregnancy were 634±228 ng/ml and in preeclamptic patients were 1426±430 ng/ml, [7] but this study did not include estimation of fibrinogen levels.

The rationale of our study was to compare D Dimers and fibrinogen levels in the third trimester of normal pregnancy versus pregnancy complicated by gestational hypertension or preeclampsia. Literature shows that these markers of the hemostatic system increase during normal pregnancy and they should increase further in pregnancies complicated by hypertension. Moreover, fibrinogen levels increase during normal pregnancy, so, if they increase further in hypertensive pregnancies, the risk of thromboembolism will be increased and such pregnancies should be closely monitored. This study will be a positively significant contributor to national data on these markers of the hemostatic system in normal and complicated pregnancies.

Materials and Methods

This Descriptive cross-sectional study was carried out in the Department of Hematology, Holy Family Hospital, Rawalpindi from April 2018 to 30th September 2018.Using the WHO sample size calculator, keeping confidence level 95%, a margin of error 0.1, mean fibrinogen in preeclampsia 654.5[6], standard deviation 131.74 mg/dl [6, the] sample size is 100. Proportionate sampling was done, 50 normal pregnant women and 50 women with gestational hypertension or preeclampsia were selected. Sampling technique used is Non-probability, consecutive sampling. Women of reproductive age group (15-49 years) with the gestational age of 28 to 40 weeks with and without gestational hypertension or preeclampsia (as per operational definitions) were included. Patients with a family or personal history of thromboembolic disease, varicose veins, any malignancy, liver disease (abnormal liver function tests) or renal disease (abnormal creatinine) and patients with current infection or fever of >38 °C were excluded.

Approval from the Institutional Research Forum of Rawalpindi medical university was taken. Informed consent was obtained. Data regarding demographics (name and age) and gestational age were also obtained. Blood sample from each patient was obtained under aseptic measures by using a 3cc BD syringe into a blue vacutainer containing trisodium citrate yielding a final concentration of 9 parts blood to 1 part anticoagulant. These tubes were then immediately centrifuged at 4000rpm for 15 min to prepare platelet-poor plasma for measurement of d-dimers and fibrinogen within the hospital laboratory. D-dimers were measured on freshly separated plasma within 4 hours of the blood collection by D dimer latex kit. The fibrinogen concentration was measured using Clauss fibrinogen assays. Reports were assessed by the researchers themselves and all the information was recorded in the study proforma.

The collected data was entered and analyzed through SPSS version 22.0. Means and standard deviation were calculated for quantitative variables i.e. age, gestational age, D-dimers, and fibrinogen. The mean values of d dimers and fibrinogen levels were compared between normal pregnant women and women with gestational hypertension or preeclampsia using an independent sample's t-test at a 5% level of significance. A p-value of ≤ 0.05 was taken as statistically significant. Effect modifiers like age and gestational age were controlled through stratification. Post-stratification independent sample t-test was applied.

Results

The age range in this study was from 15 to 49 years with a mean age of 27.80 ± 3.94 years. The majority of the women i.e. 82 (82.0%) were between 15 to 30 years of age. Mean Gestational age was 31.85 ± 3.78 weeks. In the study, mean levels of D dimers and fibrinogen among pregnant patients in the third trimester were

240.0 ± 112.82 ng/ml and 281.65 ± 51.85 mg/dl respectively.

In this study, mean D-dimers during normal pregnancy were 220.0±60.61 ng/ml and in PIH or preeclamptic patients were 260.0±145.69 ng/ml with a p-value of 0.076 as shown in Table III. Mean fibrinogen levels during normal pregnancy were 280.0±49.72 mg/dl and in PIH or preeclamptic patients were 283.30±54.34 mg/dl with a p-value of 0.752 as shown in Table I.

Stratification of mean levels of D dimers and fibrinogen with respect to age groups is shown in Tables II respectively. Stratification of mean levels of D dimers and fibrinogen with respect to gestational age is shown in Tables III respectively.

Table I: Comparison of mean levels of D dimers and fibrinogen in normal pregnant women versus pregnant women with gestational hypertension or pre-eclampsia

	Serum D dimer levels (ng/ml)		P-value Mean	Fibrinogen (mg/dl)		P-value
	Mean	SD		Mean	SD	
PIH or Preeclampsia	260.0	145.69	0.076	283.30	54.34	0.752
Normotensive	220.0	60.61				

Table II: Stratification of mean levels of D dimers (ng/ml) and fibrinogen (mg/dl) among pregnant patients in third trimester with respect age groups

Age groups (years)	Serum D dimer levels (ng/ml)		P-value	Fibrinogen (mg/dl)		P Value
	Mean	SD		Mean	SD	
15-30	236.59	103.65	**0.521**	280.18	53.32	**0.549**
31-49	255.56	150.38		288.33	45.28	

Table III: Stratification of mean levels of D dimers and fibrinogen among pregnant patients in third trimester with respect gestational age

Gestational Age (weeks)	Serum D dimer levels (ng/ml)		P-value	Fibrinogen (mg/dl)		P Value
	Mean	SD		Mean	SD	
28-34	226.03	81.70		283.70	**50.23**	**0.519**
35-40	277.78	167.18		276.11	56.61	

Discussion

Pregnancy is physiological state, systemic changes occur virtually in every organ system including blood. Changes in the coagulation system result from a hypercoagulable state. The main culprit is the increase in plasma fibrinogen levels and other coagulation factors. Normal plasma fibrinogen levels are 200-400 mg/dl, whereas fibrinogen levels reach up to 600 mg/dl in pregnancy. Factors II, VII, VIII, IX, and X increase whereas Protein C, protein S, and antithrombin III are decreased. All these processes along with decreased fibrinolytic activity lead to a hypercoagulable state. Increased intravascular coagulation functions to keep uteroplacental interface. These changes in blood coagulation prevent excessive bleeding by effective hemostatic mechanisms after placental separation.[11] Pre-eclampsia is characterized by microvasculature fibrin deposition. The marker used for fibrin degradation in vivo is D-dimer. Therefore, D-dimer is used as an important marker in the diagnosis of thrombotic conditions because of its high negative predictive value.

A study conducted in India showed that mean fibrinogen levels in normal pregnant women were 491.52±81.7 mg/dl and in preeclamptic women were 654.5±131.74 mg/dl.[6] Another study showed that mean D-dimers during normal pregnancy were 634±228 ng/ml and in preeclamptic patients were 1426±430 ng/ml,[7] but this study did not include estimation of fibrinogen levels.

In a study, D-dimer levels of pre-eclamptic women as compared to normal controls were significantly high.[12] In a case-control study[13], preeclampsia and normal pregnancy groups were compared for fibrinogen and D-dimer. The mean levels of plasma fibrinogen (358.30±138.6 vs. 280.00±72.8 mg/dL, P.value <0.001) and plasma D-dimer (0.364±0.38vs 0.148±0.06 mg/L, P.value < 0.000) were significantly higher in the

preeclampsia group as compared to normal pregnancy. The percentage of high D-dimer was found in (48%) and (6%), while high fibrinogen was found in (48%) and (18%) of patients and control respectively.[12]

A study done by Williams VK et al[13] in South Australia in the evaluation of fibrinogen concentration in preeclampsia and normal pregnant women found fibrinogen levels higher in women with preeclampsia compared with normal pregnancies ($P < 0.05$). Pinheiro Mde B et al[14] in Brazil, showed that increased plasma D- dimer is associated with preeclampsia in the third trimester of gestation in comparison to normotensive pregnant subjects. Another study done by Zhou H. et al[15] in China, estimated plasma D-dimer in preeclampsia and showed the great significance of plasma D-dimer levels that appear in the second and third trimesters in pregnant women with hypertension.

Assays for the measurement of fibrin degradation products have become a notable diagnostic tool due to their ease in the detection of hypercoagulability states. Fibrinogen and D-dimers, both are usually used. Increased plasma D-dimer levels were seen in the last trimester of normal and complicated pregnancies by some authors[16-20] but not by others.[21] And a suggestion was made for the predictive role of D-dimer concentration for the development of preeclampsia.[21] Intravascular fibrin deposition occurring in uteroplacental circulation, is the earliest and most consistent alteration in blood coagulation function noted during pregnancy. Furthermore, there is a fivefold increase in fibrin deposition during pregnancy compared to the non-pregnant state which logically is accompanied by a significant increase in fibrinolysis to create homeostasis.[22, 23.]

Limitations of the Study:

- This was a single-center study which could lead to observation bias and thus the results cannot be generalized to the entire Pakistani population. We should conduct this study on a large sample size.
- We only assessed two markers of hemostatic profile namely D dimers and fibrinogen. Many other coagulation factors were not assessed.
- Patients with high levels of D dimers and/or fibrinogen were not followed up for the probability of having thromboembolism.
- The anticoagulant mechanisms were not assessed in the current study.
- Some of the risk factors leading to hypercoagulability were based on the history given by the patients. Some patients were unable to provide proper history due to a lack of education and knowledge

Conclusion

This study concluded that mean levels of D dimers and fibrinogen in pregnant women with gestational hypertension or pre-eclampsia are higher as compared to normotensive women but the difference is not statistically significant.

Conflict of Interest: Authors declare no conflict of interest.

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D. Conception/Study/Designing/Planning
E. Active Participation in Active Methodology
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