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Pathology

Assesment of Prothrombin Time, APTT and Fibrin Degradation Product as Predictor of DIC & HELLP Syndrome in Case of Pregnancy Induced Hypertension

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Original Research Article

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Abstract: Pregnancy induced hypertension (PIH) is divided into three clinical types: pre-eclampsia, eclampsia, and gestational hypertension. It has been recorded that the maternal utero-placental blood flow decreases in pre-eclampsi because of maternal vasospasm. Reduced maternal utero placental blood flow leading indirectly to constriction of fetal stem arteries has been associated with the changes seen in the placentas of women with pre-eclampsia. Maternal vasospasm leads to fetal hypoxia. The agent responsible for vasospasm has still not been isolated precisely, but it seems certain to be humoral in origin. To assess the Prothrombin time, APTT and Fibrin degradation product among cases with Pregnancy Induced hypertension (study group) as predictor of DIC & HELLP syndrome. To perform Prothrombin time, APTT and Fibrin degradation product in patient of PIH and control. To assess the profile as predictor of DIC and HELLP syndrome among them. There was high sensitivity, specificity of PT, APTT and FDP in predicting DIC, HELLP and in differentiating DIC from HELLP.
Keywords: APTT, DIC & HELLP Syndrome, Pregnancy & Hypertension.

INTRODUCTION

Pregnancy induced hypertension (PIH) is divided into three clinical types: pre-eclampsia, eclampsia, and gestational hypertension. It has been recorded that the maternal utero-placental blood flow decreases in pre-eclampsia [1] because of maternal vasospasm [2].

Reduced maternal utero placental blood flow leading indirectly to constriction of fetal stem arteries has been associated with the changes seen in the placentas of women with pre-eclampsia. Maternal vasospasm leads to fetal hypoxia. The agent responsible for vasospasm has still not been isolated precisely, but it seems certain to be humoral in origin [3].

In PIH, resistance to flow in utero-placental circulation is increased, affecting the growth of placenta in terms of weight, thickness, surface area, volume and location. These placental abnormalities ultimately result in reduction of fetal weight[4]. So,its examination gives a clear idea of what had happened with it, when it was in the mother womb and what is going to happen with the fetus in future[5]. Several studies were done to find out the significance of placental location in the uterine cavity.Placental location has been found to correlate with fetal position and presentation, length of gestation, course of labour, presence of preeclampsia and pregnancy outcome[6]. Several methods have been used to document placental location, including manual exploration of theuterus, soft tissue x-ray films, and isotopic placentagraphy[7]. In the past two decades, ultrasonography has proved to be the safest, easiest, and most accurate method for assessing placental location[8].

AIMS AND OBJECTIVES

Aim

To assess the Coagulation Profile among cases with Pregnancy Induced hypertension (study group) as predictor of DIC & HELLP syndrome.

OBJECTIVES

- To perform Prothrombin time, APTT and FDP in patient of PIH and control.
- To assess the profile as predictor of DIC and HELLP syndrome among them.

MATERIAL AND METHODS

Study site

Department of Pathology of Index Medical College, Indore.

Study population

This study included 100 patients (50 PIH and 50 control) within the age group of 18 to 35 yrs after 20 weeks period of gestation that were admitted in the antenatal ward of the Department Of Pathology of Index Medical college, Indore.

Study design: Case-control

Study duration: One year

Inclusion criteria

Patients other than PIH were excluded from the study.

Exclusion criteria

Women with previous h/o HTN , D.M., h/o recurrent abortion, multiple fetuses, previous hepatic or renal disease, idiopathic thrombocytopenic purpura, any bleeding diathesis, immunosuppressant or h/o any illicit drug wereexcluded from this study. Women who are on treatment for PIH.

METHODS

Blood sample collection

Bloodcollected from all the enrolled patients of PIH not on any treatment. Whole blood sample obtained by puncture of the anterior cubital vein. The blood sample was obtained without a pressure cuff, allowing blood to enter the syringe by continuous free flow by the negative pressure from an evacuated tube. The 22 Gauge size needle and good quality 10 ml disposable plastic syringe was used for the collection of blood**.**

Collected blood sample then was run in automated cell counter for total platelet count, and also in automated coagulation analyzer for determination of PT and aPTT.

Call coagulation studies3.6 ml of bloodcollected in plastic Vial containing 0.4 ml sodium citrate2 ml of bloodcollected in EDTA a vial containing 2.4 mg anhydrous di-potassium salt of ethylene Tetra acetic acid. From each patient above samples received were investigated under following heads-

Coagulation studies

- Prothrombin time - Prothrombin time is the time required for Plasma to clot after tissue thromboplastin find optimal amount of calcium chloride have been added.
- Activated partial thromboplastin time (APTT) it measure the procoagulant activity of plasma. The partial thromboplastin time is he substitute of platelet factor 3 and therefore APTT can not measure this activity .it also does not measure factor VII and XIII. An activator is added to the partial thromboplastin reagent to produce maximal contact activation and standardize the activation.
- Fibrin degradation product level (FDP) - performed by tulip XL FDP Kit method for quantitative and semi quantitative latex slide test for detecting cross fibrin degredation product in human plasma.

Handling of samples and reagent

- All plasma sample were kept in plastic vials & tubes.
- Processing of test sample and coagulation studies were performed within 2 hours of collection of sample.
- all collection performed by using automatic pipette and disposable tips.
- The test were performed at 37’c with clean and dry round bottom glass tube.

Control plasma

For making control pooled plasma at least 5 blood samples from healthy subject should be pooled and processed in the same way as test samples. Fresh plasma should not be more than 1 hour old and blood sample should have been kept in refrigerator at 4-8’c control plasma should be makes ones I week and stored at 20’c.

STATISTICAL ANALYSIS

The results are presented in frequencies, percentages and mean±SD. Chi-square test was used to compare categorical variables. One way analysis of variance (ANOVA) followed by Tukey’s post-hoc tests was used to compare the continuous variables between cases and controls The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of different parameters was calculated in predicting DIC and HELLP. The p-value<0.05 was considered significant. All the analysis was carried out on SPSS 16.0 version (Chicago, Inc., USA).

OBSERVATIONS AND RESULTS

The mean age of cases and controls was 23.98±3.32 and 24.10±1.90 years respectively.Majority of both cases (70%) and controls (80%) belonged to rural area. More than one third of cases (46%) and 68% controls G1 gravida. Both SBP and DBP were significantly (p=0.0001) higher among cases compared to controls. One stage prothrombin time was significantly (p=0.0001) higher among cases (23.88±9.36) than controls (11.88±0.87). Activated partial thromboplastin time was significantly (p=0.0001) higher among cases (42.70±8.38) than controls (30.88±2.35). Live birth was in 80% of cases and in all the controls with significant association (p=0.001). HELLP syndrome was in 28% of cases and

DIC was in 12% of the cases. There was significant (p=0.0001) difference in one stage prothrombin time among the complications. There was significant (p=0.0001) difference in activated partial thromboplastin time among the complications. Fibrin degradation product level was ≥200 in 80% of cases and in 10% of controls. FDP of ≥200 was 36 times significantly (p=0.0001) higher in cases than controls.

On comparison of PT with complication among cases. The analysis of variance showed that there was significant (p=0.0001) difference in PT among the complications. The post-hoc tests revealed that PT was significantly (p<0.05) different with each other.

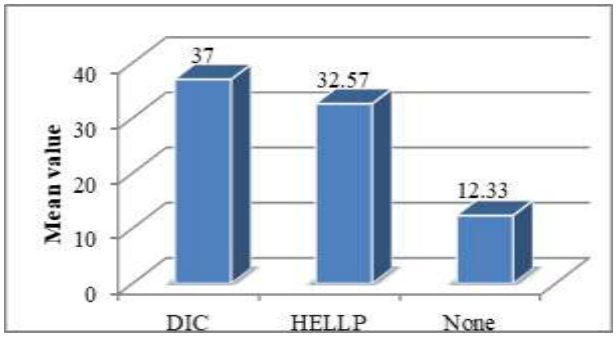

Fig-1: Comparison of prothrombin time with complication among the cases

On comparison of activated partial thromboplastin time with complication among cases. The analysis of variance showed that there was significant (p=0.0001) difference in activated partial thromboplastin time among the complications. The post-hoc tests revealed that activated partial thromboplastin time was significantly (p<0.05) different with each other.

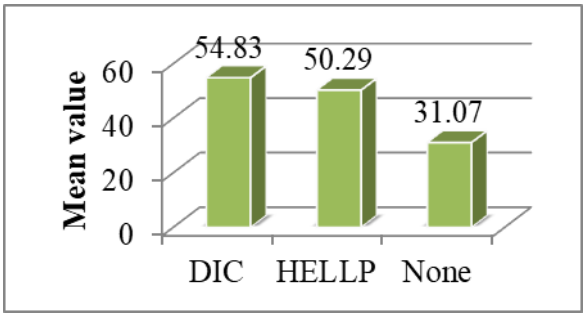

Fig-2: Comparison of Activated partial thromboplastin time with complication among the cases

On comparison of Fibrin degradation product (FDP) level with complication among cases. Both DIC and HELLP syndrome were higher among whom Fibrin degradation product (FDP) level was ≥200 than <200 and the association was statistically significant (p=0.001).

There was high sensitivity, specificity of PT, APTT and FDP in predicting DIC, HELLP and in differentiating DIC from HELLP.

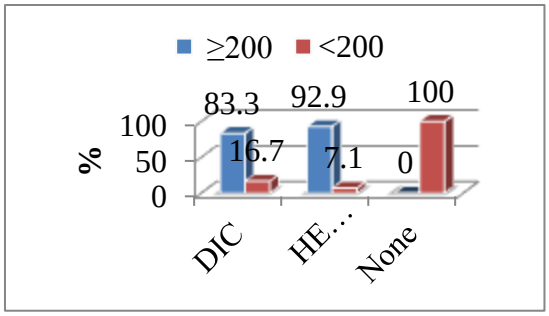

Fig-3: Comparison of Fibrin degradation product level with complication among the cases

Table-1: Predictive value of PT, APTT and FDP in predicting DIC

Coagulation parameters	DIC				Total		Predictive value (%)				
	Yes		No				Sensitivity	Specificity	PPV	NPV	Accuracy
	No.	%	No.	%	No.	%					
PT											
>25	6	16.7	1	2.8	7	19.4	100.0	96.7	85.7	100.0	97.2
≤25	0	0.0	29	80.6	29	80.6					
Total	6	16.7	30	83.3	36	100.0					
APTT											
>50	6	16.7	0	0.0	6	16.7	100.0	100.0	100.0	100.0	100.0
≤50	0	0.0	30	83.3	30	83.3					
Total	6	16.7	30	83.3	36	100.0					
FDP											
≥200	5	13.9	22	61.1	27	75.0	83.3	80.0	18.5	98.9	80.2
<200	1	2.8	8	22.2	9	25.0					
Total	6	16.7	30	83.3	36	100.0					

%age is from total number of cases

Table-1 shows the predictive value of PT, APTT and FDP in predicting DIC. There was high sensitivity, specificity of PT, APTT and FDP in predicting DIC.

Table-2: Predictive value of PT, APTT and FDP in predicting HELLP

Coagulation parameters	**DIC**				**Total**		**Predictive value (%)**				
	Yes		**No**				**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
	No.	**%**	**No.**	**%**	**No.**	**%**					
PT >15	13	29.5	18	40.9	31	70.5	92.9	40.0	41.9	92.3	56.8
≤15	1	2.3	12	27.3	13	29.5					
Total	14	31.8	30	68.2	44	100.0					
APTT >40	13	29.5	3	6.8	16	36.4	92.9	90.0	81.3	96.4	90.9
≤40	1	2.3	27	61.4	28	63.6					
Total	14	31.8	30	68.2	44	100.0					
FDP ≥200	13	29.5	22	50.0	35	79.5	92.9	26.7	37.1	88.9	47.7
<200	1	2.3	8	18.2	9	20.5					
Total	14	31.8	30	68.2	44	100.0					

%age is from total number of cases.

Table-2 shows the predictive value of PT, APTT and FDP in predicting HELLP. There was high sensitivity, specificity of PT, APTT and FDP in predicting HELLP.

Table-3: Predictive value of PT, APTT and FDP in differentiating DIC from HELLP

Coagulation parameters	**Complication**				**Total**		**Predictive value (%)**				
	DIC		**HELLP**				**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
	No.	**%**	**No.**	**%**	**No.**	**%**					
PT											
>15	4	20.0	4	20.0	8	40.0	66.7	71.4	50.0	83.3	70.0
≤15	2	10.0	10	50.0	12	60.0					
Total	6	30.0	14	70.0	20	100.0					
APTT											
>40	6	30.0	6	30.0	12	60.0	100.0	57.1	50.0	100.0	70.0
≤40	0	0.0	8	40.0	8	40.0					
Total	6	30.0	14	70.0	20	100.0					
FDP											
≥200	5	25.0	13	65.0	18	90.0	83.3	7.1	27.8	50.0	30.0
<200	1	5.0	1	5.0	2	10.0					
Total	6	30.0	14	70.0	20	100.0					

%age is from total number of cases

Table- 3 shows the predictive value of PT, APTT and FDP in differentiating DIC from HELLP. Reasonable sensitivity, specificity of PT, APTT and FDP was found in differentiating DIC from HELLP.

DISCUSSION

A part from general profile of cases and controls, the following parameters were also studied in this study:

Prothrombin time, activated partial thromboplastin time and fibrin degradation product level. The present study revealed that all the coagulation parameters were higher in DIC compared to HELLP. Jahromi and Rafiee *et al*.[9] found that among their 25 PE patients, 3 cases showed evidence of disseminated. Intravascular coagulation (DIC) in their hospital course and had simultaneous prolongation of APTT and one patient had an elevated FDP.

In the present study, there was high sensitivity, specificity of PT, APTT and FDP in predicting DIC. There was high sensitivity, specificity of PT, APTT,thrombin time and FDP in predicting HELLP. Reasonable sensitivity, specificity of PT, APTT and FDP was found in differentiating DIC from HELLP. Only one study could be found in assessing the predictive values. Offer et al (2014) showed that PT difference had an area under the curve (AUC) of 0.96 ($p<0.001$), and a PT difference ≥ 1.55 had an 87% sensitivity and 90% specificity for the diagnosis of DIC; 1) the platelet count had an AUC of 0.87 ($p<0.001$), an 86% sensitivity and 71% specificity for the diagnosis of DIC; 2) fibrinogen concentrations had an AUC of 0.95 ($p<0.001$) and a cutoff point ≤ 3.9 g/L had a sensitivity of 87% and a specificity of 92% for the development of DIC; and 3) The pregnancy adjusted DIC score had an AUC of 0.975 ($p<0.001$) and at a cutoff point of ≥ 26 had a sensitivity of 88%, a specificity of 96%, a LR(+) of 22 and a LR(−) of 0.125 for the diagnosis of DIC.

Suresh *et al*. [10] observed that mild PE did not reveal any significant changes in coagulation parameters as compared to healthy pregnant women. However, severe PE and eclampsia were characterized by coagulation abnormalities indicating intravascular coagulation. Platelet count and aPTT had predictive value in screening for consumptive coagulopathy in the severe cases of PE and eclampsia.

In another study by Awad-Elkareem *et al.*[11], the mean Fibrinogen level in the three studied groups was 3.96±0.81, 3.80±0.40, and 3.36±0.32 in PE, normal pregnant, and non-pregnant group; respectively. The mean PT was 14.20±3.48, 12.90±1.13, and 11.73±1.55, whereas mean APTT was 38.32±7.71, 35.60±6.96, and 33.56±6.26 ; respectively. The study found that PT (P; 0.01, 0.06), APPT (P; 0.02, 0.04) of PE group was significantly higher than normal pregnant and non-pregnant groups; respectively.

Preeclampsia is an idiopathic multisystem disorder specific to human pregnancy and the puerperium[12]. Hematological abnormalities such as thrombocytopenia and decrease in some plasma clotting factors may develop in preeclamptic women[13]. Subtle changes suggesting disseminated intravascular coagulation (DIC) is one of the serious outcome of preeclampsia. Thus, coagulation testing is to be done in these patients to rule out DIC and HELLP (hemolysis, enzyme elevation and low platelet) syndrome. From the historical point of view, earlier it was stated that only serial measurements of platelet count was adequate for intrapartum screening. Later, combination of platelet count and aPTT, platelet count and liver function tests, platelet count and lactatedehydrogenase, platelet count and antithrombin were suggested for early detection and screening of the patients with preeclampsia [14].

Since plasmin has the potential to degrade fibrinogen leading to deleterious consequences, the fibrinolytic activity is limited by following factors:

- Plasminogen activator inhibitor - It is the main physiological inhibitor of fibriolysis and acts by inhibiting t-PA and u-PA irreversibly.
- TAFI - It is a plasma proenzyme synthesized by liver and activated by thrombin. It decreases the affinity of plasminogen to fibrin and augments the action of anti-trypsin in inhibiting plasmin.
- Plasmin inhibitors - α2 antiplasmin and α2Macroglobulin are the glycoproteins that exert action by virtue of plasmin inhibition.

The findings of this study indicate that investigation of PT, APTT and FDP are useful to detect an early ongoing coagulability in patients with PIH who will develop DIC and HELLP syndrome. However, more studies with large sample size should be conducted to screen and verify which coagulation parameters can predict the development of coagulability in such patients.

CONCLUSIONS

The present study was conducted in the Department of Pathology of Index Medical College, Indore with the objective to assess the Coagulation Profile among cases with Pregnancy Induced hypertension (cases) as predictor of DIC & HELLP syndrome. A total of 50 cases and 50 controls were included in the study.The following are the findings of this study:

- prothrombin time was significantly ($p=0.0001$) higher among cases (23.88±9.36) than controls (11.88±0.87). Activated partial thromboplastin time was significantly ($p=0.0001$) higher among cases (42.70±8.38) than controls (30.88±2.35). Fibrin

degradation product level was ≥200 in 80% of cases and in 10% of controls. FDP of ≥200 was 36 times significantly(p=0.0001) higher in cases than controls. Live birth was in 80% of cases and in all the controls with significant association (p=0.001).

- HELLP syndrome was in 28% of cases and DIC was in 12% of the cases.
- There was significant (p=0.0001) difference in prothrombin time among the complications.
- There was significant (p=0.0001) difference in activated partial thromboplastin time and FDP among the complications.
- There was high sensitivity, specificity of PT, APTT and FDP in predicting DIC, HELLP and in differentiating DIC from HELLP.

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