

Original Research Article

Coagulation Profile in Pregnancy Induced Hypertension to Predict DIC and HELLP Syndrome

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Abstract

Background and Aim: Hypertensive disorders of pregnancy commonly known as Pregnancy Induced Hypertension (PIH), affects about 10% of all pregnant women around the world. A variety of haematological abnormalities may occur in women with PIH, thrombocytopenia being the most common. There is also a definite exaggeration of the hypercoagulable state during PIH due to increase in coagulation factors like fibrinogen. A strong relationship exists between the two most important causes of maternal mortality and morbidity worldwide: Preeclampsia and Post-partum haemorrhage. The aim of this study was to find out the changes that occur in the coagulation profile and platelet indices in PIH as compared to that in normal pregnancy and if they can be used as a reliable indicator of the onset and severity of Disseminated Intravascular Coagulopathy (DIC) and HELLP Syndrome. Method: A total of hundred pregnant women (50 PIH and 50 control) within the age group of 18 to 35 years after 20 weeks period of gestation were admitted in the antenatal ward of the Department of Obstetrics and Gynaecology of Index Medical College, Indore. Their complete blood picture with platelets count and coagulation profile were done to compare with normal control pregnant women. Result: Bleeding time (BT), Clotting time (CT), one stage Prothrombin time (PT), activated partial Thromboplastin time (aPTT) and Thrombin time (TT) was significantly higher amongst cases than in controls. Conclusion: Thus, authors came to the conclusion that platelet indices and coagulation profile can be used as a reliable early indicator of onset and severity of DIC and HELLP Syndrome.

Keywords: Pregnancy induced hypertension; coagulation profile; Disseminated Intravascular Coagulopathy; HELLP Syndrome.

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-eclampsia¹ because of maternal vasospasm.² Reduced maternal utero-placental

blood flow leading indirectly to constriction of foetal stem arteries has been associated with the changes seen in the placentas of women with pre-eclampsia. Maternal vasospasm leads to foetal 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 foetal 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 foetus 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 foetal 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 the uterus, soft tissue x-ray films, and isotopic placentography.⁷ In the past two decades, ultrasonography has proved to be the safest, easiest, and most accurate method for assessing placental location.⁸

Hypertensive disorders during pregnancy are associated with high maternofetal mortality and morbidity in both underdeveloped and developed countries.⁹ Approximately 70% of hypertensive disorders are due to gestational hypertension, this condition is called pre-eclampsia.¹⁰

Pre-eclampsia (PE) is defined as hypertension associated with proteinuria. Proteinuria is defined as the excretion of 300 mg or more of proteins in 24 h or proteinuria with a concentration of 300 mg/L or more of proteins ($\geq 1 +$ dipstick) in two different urine samples with a range of at least 4 to 6 h.¹¹ PE can manifest as swellings in face, hands, lower limbs or generalized swelling. The diagnosis is usually made after the 20th week of gestation, although early cases may occur in the hydatidiform mole or foetal hydrops.

Severe pre-eclampsia has been defined as SBP ≥ 160 mmHg and/or DBP ≥ 110 mmHg associated with proteinuria; hypertension associated with severe proteinuria (above 2.0 g in 24 h); hypertension associated with multiple organ involvement (pulmonary edema and oliguria <500 mL/day); and hypertension associated with persistent symptoms (visual, cerebral and persistent epigastric or right upper quadrant pain) or altered laboratory tests (platelet count $<100,000$ per μ L and hepatic enzymes).¹¹

Eclampsia is defined by expression of one or more seizures or coma in pregnant women with gestational hypertension or pre-eclampsia, in the absence of neurological diseases and HELLP syndrome, which occurs in the presence of thrombocytopenia, microangiopathic hemolysis and liver dysfunction in pregnancy toxemia. It can

occur during pregnancy, labour and immediately after delivery.

Foetal neonatal jeopardy results primarily from compromised placental perfusion and the need for preterm delivery in severe cases. In developed countries, up to 25% of all prenatal deaths are attributable to hypertensive disorders of pregnancy, the major maternal hazards are the consequences of severe hypertension, grandmal seizures and damage to other end organs. In many areas of the world, hypertensive disorders of pregnancy are not most common cause of maternal death because with modern management, preeclampsia can be ameliorated and eclampsia is largely prevented.¹²

Changes in coagulation profile that occur in normal pregnancy includes the biochemical adaptation especially the haematological changes that occurs in response to pregnancy are profound the levels of several blood coagulation factors are increased during pregnancy. Coagulation factors are increased during pregnancy. Plasma fibrinogen increases about 65% late in pregnancy. The increase in fibrinogen concentration contributes significantly to the striking increase in ESR. Other clotting factors that increase appreciable during normal pregnancy are factors VII, VIII, IX and X. prothrombin and factors V and XII do not change. Whereas, factors XI and XIII decreases slightly. There is moderate decrease in platelet count as pregnancy progresses.

Disseminated Intravascular Coagulation (DIC) is always a secondary phenomenon trigger by specific obstetrics complications like Preeclampsia, Eclampsia, Abruption placenta, intrauterine infection, retained dead foetus, placenta accrete, Hydatidiform mole, prolonged shock and amniotic fluid embolism.¹³

PIH may also result in a variety of hematological aberrations.¹⁴ Thrombocytopenia is the most common hematological abnormality found in pre-eclampsia and eclampsia.¹⁵ It is a strong indicator of severity of PIH. Other coagulation abnormalities such as prothrombin time (PT), activated partial thromboplastin time (aPTT), fibronectin time, and antithrombin III level are more sensitive.¹⁶

Alteration of coagulation factors increases the risk of bleeding complications in pre-eclampsia and eclampsia. Hemorrhages are a major problem where it is the main cause of maternal mortality, which usually occur during operative delivery or regional anesthesia procedure. To reduce the maternal morbidity and mortality need of accurate and rapid biochemical tests to detect the complications of pre-eclampsia and eclampsia including HELLP syndrome. Detecting the severity of PIH disorders,

help in the better management of patients. Hence, the present study has been undertaken to correlate coagulation parameters with the severity of PIH, which helped us in the early management of PIH before it worsens.¹⁷

HELLP syndrome, a variant of severe pre-eclampsia, was first described in 1954 by Pritchard and identified as a distinct clinical entity by Louis Weinstein in 1982. HELLP syndrome is as haemolysis (abnormal peripheral smear or raised total bilirubin $>20.5 \mu\text{mol/l}$), raised liver enzyme activity (elevated aspartate aminotransferase $>70 \text{ IU/l}$ or raised glutamyltransferase $>70 \text{ IU/l}$) and low platelets ($<100\ 000/\text{ml}$). Sometimes HELLP syndrome leads to disseminated intravascular coagulation (DIC), which can make emergency surgery a serious challenge.^{18,19}

The present study was conducted to assess the Coagulation Profile among cases with Pregnancy Induced hypertension (study group) as predictor of DIC and HELLP syndrome.

Methods

The study was conducted in Department of Obstetrics and Gynaecology of Index Medical College, Indore. This study included 100 patients (50 PIH and 50 control) within the age group of 18 to 35 years after 20 weeks period of gestation that were admitted in the antenatal ward. This was a case-control study for a duration of one year.

Inclusion criteria were 1) Pregnant women of age group 18 to 35 years 2) 20 weeks or plus period of gestation. Exclusion criteria were 1) Women with previous h/o HTN, D.M., 2) h/o recurrent abortion, multiple foetuses, 3) previous hepatic or renal disease, 4) idiopathic thrombocytopenic purpura, any bleeding diathesis, immunosuppressant or 5) h/o any illicit drug, and 6) Women who were on treatment for PIH.

Blood collected 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 a PTT, Fibrin degradation product level and thrombin time.

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 $4-8^\circ\text{C}$ control plasma should be makes ones I week and stored at 20°C .

The results are presented in frequencies, percentages and Mean \pm 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 receiving operating curve (ROC) analysis was performed. The p-value <0.05 was considered significant. All the analysis was carried out on SPSS 16.0 version (Chicago, Inc., USA).

Results

Table 1 and Fig. 1 shows the distribution of cases and controls according to age. The mean age of cases and controls was 23.98 ± 3.32 and 24.10 ± 1.90 years respectively. There was no significant ($p>0.05$) difference in the age between the groups.

Table 1: Distribution of Cases and Controls According to Age.

Groups	Age in years (Mean \pm SD)	Min.-Max.
Cases	23.98 ± 3.32	19-32
Controls	24.10 ± 1.90	21-28
p-value ¹	0.82	

¹Unpaired t-testw

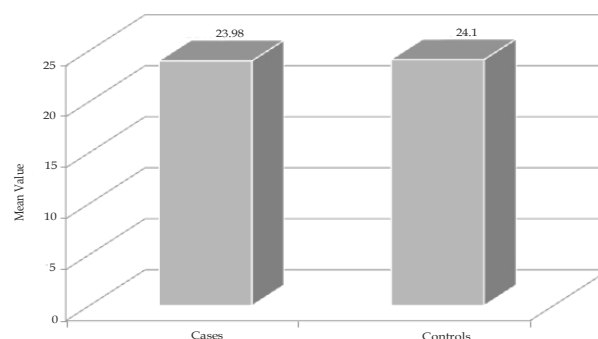


Fig. 1: Distribution of Cases and Controls According to Age.

Table 2 and Fig. 2 shows the distribution of cases and controls according to gravida. More than one third of cases (46%) and 68% controls G1 gravida. There was no significant ($p>0.05$) difference in gravida between the groups.

Table 2: Distribution of Cases and Controls According to Gravida.

Gravida	Cases (n=50)		Controls (n=50)		p-value ¹
	No.	%	No.	%	
G1	23	46.0	34	68.0	0.06
G2	18	36.0	13	26.0	
G3	5	10.0	3	6.0	
G4	4	8.0	0	0.0	

¹Chi-square test

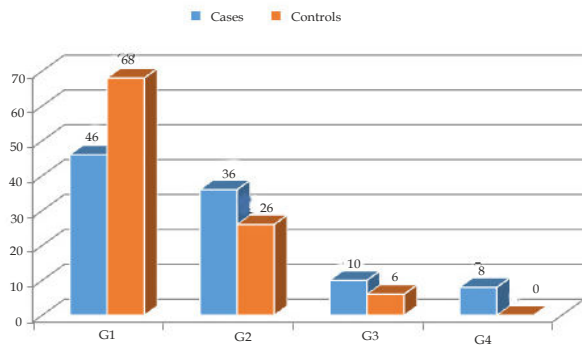


Fig. 2: Distribution of Cases and Controls According to Gravida.

Table 3 and Fig. 3 shows the comparison of platelet count between cases and controls. Platelet count was insignificantly ($p>0.05$) lower among cases (1.39 ± 0.42) compared to controls (2.65 ± 0.65).

Table 3: Comparison of Platelet Count Between Cases and Controls.

Groups	Platelet count (Mean \pm SD)
Cases	1.39 ± 0.42
Controls	2.65 ± 0.65
p-value ¹	0.62

¹Unpaired t-test

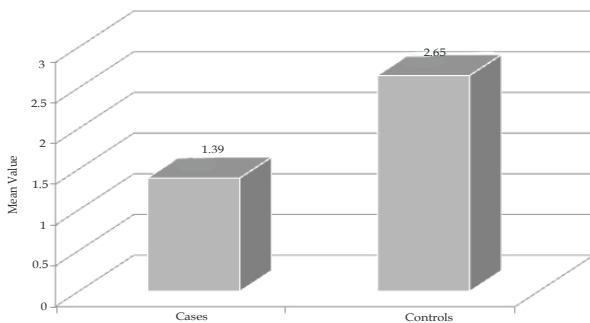


Fig. 3: Comparison of Platelet Count Between Cases and Controls.

Table 4 and Fig. 4 shows the comparison of one stage prothrombin time between cases and controls. One stage prothrombin time was significantly ($p=0.0001$) higher among cases (23.88 ± 9.36) than controls (11.88 ± 0.87).

Table 4: Comparison of One Stage Prothrombin Time Between Cases and Controls.

Groups	One stage prothrombin time (Seconds) (Mean \pm SD)
Cases	23.88 ± 9.36
Controls	11.88 ± 0.87
p-value ¹	0.0001*

¹Unpaired t-test, *Significant

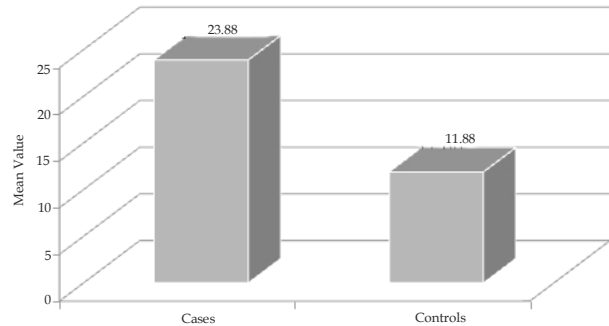


Fig. 4: Comparison of One Stage Prothrombin Time Between Cases and Control

Table 5 and Fig. 5 shows the comparison of activated partial thromboplastin time between cases and controls. Activated partial thromboplastin time was significantly ($p=0.0001$) higher among cases (42.70 ± 8.38) than controls (30.88 ± 2.35).

Table 5: Comparison of Activated Partial Thromboplastin Time Between Cases and Controls.

Groups	Activated partial thromboplastin time (Seconds) (Mean \pm SD)
Cases	42.70 ± 8.38
Controls	30.88 ± 2.35
p-value ¹	0.0001*

¹Unpaired t-test, *Significant

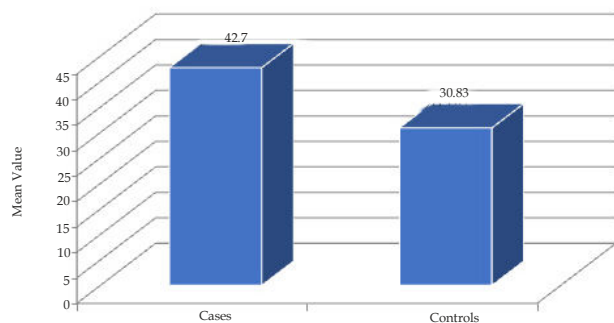


Fig. 5: Comparison of Activated Partial Thromboplastin Time Between Cases and Controls.

Table 6 and Fig. 6 shows the comparison of thrombin time between cases and controls. Thrombin time was significantly ($p=0.0001$) higher among cases (16.66 ± 2.89) than controls (12.78 ± 0.91).

Table 6: Comparison of Thrombin Time Between Cases and Controls.

Groups	Thrombin time (Seconds) (Mean \pm SD)
Cases	16.66 \pm 2.89
Controls	12.78 \pm 0.91
p-value ¹	0.0001*

¹Unpaired t-test, *Significant

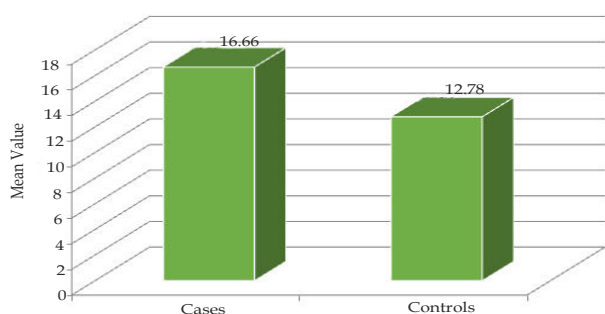
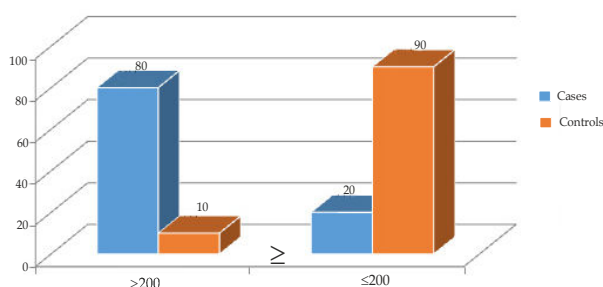
**Fig. 6:** Comparison of Thrombin Time Between Cases and Controls.

Table 7 and Fig. 7 shows the comparison of fibrin degradation product level between cases and controls. 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 (OR=36.00, 95% CI=11.34-114.25).

Table 7: Comparison of Fibrin Degradation Product (Fdp) Level (Ng/Ml) Between Cases and Controls.

FDP	Cases (n=50)		Controls (n=50)		OR (95%CI)	p-value ¹
	No.	%	No.	%		
≥ 200	40	80.0	5	10.0	36.00 (11.34-114.25)	0.0001*
< 200	10	20.0	45	90.0	1.00 (Ref.)	

¹Chi-square test, *Significant

**Fig. 7:** Comparison of Fibrin Degradation Product Level (Ng/Ml) Between Cases and Controls.

Discussion

In this study, the mean age of cases and controls was 23.98 ± 3.32 among the cases which is comparable

to Annam et al (2011)²⁰, Sandhya et al (2007)²¹ and Prakash et al (2006)²² studies with mean age of 24.57 ± 3.46 , 24.3 and 24.75 ± 3.360 respectively, however in Onisai et al (2009)²³ study they observed that the mean age of PIH was 29.8 years. In this study, more than one third of cases (46%) and 68% controls had G1 gravida. There was no significant ($p>0.05$) difference in gravida between the groups. This finding is comparable to other studies (Prakash et.al, 6006 with 44%; Audiebert et al, 1996 with 53.5%; and Jahromi and Rafiee, 2009 with 56% of cases.^{22,24,25}

In this study, platelet count was insignificantly ($p > 0.05$) lower among cases (1.39 ± 0.42) compared to controls (2.65 ± 0.65). This finding is comparable to the study by Meshram et al, (2014)²⁶ in which the platelet count in preeclampsia and eclampsia was significantly lower than that in normal healthy pregnant controls. The similar finding was also reported by Jambhulkar et al (2001).²⁷

In this study, one stage prothrombin time was significantly ($p=0.0001$) higher among cases (23.88 ± 9.36) than controls (11.88 ± 0.87). This finding is higher than the study by Awad-Elkareem et al (2016)²⁸ in which the mean PT was 14.20 ± 3.48 , 12.90 ± 1.13 , and 11.73 ± 1.55 in PE, normal pregnant, and non-pregnant group; respectively, the difference may be due to different socio-demographic status of the patients between the present study and their study. However, Jambhulkar et al (2001)²⁷ found prolonged PT (>14) among PIH patients.

In this study, activated partial thromboplastin time was significantly ($p=0.0001$) higher among cases (42.70 ± 8.38) than controls (30.88 ± 2.35). Similar finding was found by Meshram et al (2014)²⁶ in which the mean activated partial thromboplastin time in preeclampsia was 37.44 ± 6.60 s with $p<0.001$ which was significantly prolonged when compared with healthy controls. Similarly, in eclampsia the mean activated partial thromboplastin time was 37.69 ± 5.61 s with P value < 0.001 which is again significantly prolonged as compared to controls.

In the present study, thrombin time was significantly ($p=0.0001$) higher among cases (16.66 ± 2.89) than controls (12.78 ± 0.91). Similar finding was reported by Shetty et al (2016)²⁹ in which the TT in PIH was significantly prolonged ($P < 0.05$) compared to controls. In a study (Meshram et al, 2014)²⁶, prothrombin time was not significantly prolonged ($P>0.05$) in various severity of pregnancy induced hypertension.

In this study, 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 (OR=36.00, 95% CI=11.34-114.25). Jahromi and Rafiee et al (2009)²⁵ reported that fibrin degradation product (FDP) ($p<0.001$) were higher in preeclamptic patients. However, they didn't find statistical differences in the mean values of plasma fibrinogen between the two groups ($p>0.05$).

The present study revealed that all the coagulation parameters were higher in DIC compared to HELLP. Jahromi and Rafiee et al (2009)²⁵ 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, Thrombin time 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, thrombin time 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 cut-off 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 cut-off 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.

Conclusion

The present study was conducted in the Department of Obstetrics and Gynaecology of Index Medical College, Indore with the objective to assess the Coagulation Profile among cases with Pregnancy Induced hypertension (cases) as predictor of DIC and HELLP syndrome. A total of 50 cases and 50 controls were included in the study. The final conclusion of the study is that the mean age of cases and controls was 23.98 ± 3.32 and 24.10 ± 1.90 years respectively of which more than one third of cases (46%) and 68% controls G1 gravida. 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). Thrombin time was significantly ($p=0.0001$) higher among cases (16.66 ± 2.89) than controls (12.78 ± 0.91).

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. There was significant ($p=0.0001$) difference in thrombin time among the complications. There was high sensitivity, specificity of PT, APTT, Thrombin time and FDP in predicting DIC, HELLP and in differentiating DIC from HELLP.

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