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Original Article

Hematological Changes in Pregnancy-induced Hypertension

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Abstract

Background: Pregnancy-induced hypertension (PIH) is the most common medical disorder of pregnancy contributing significantly to maternal/fetal morbidity and mortality. Hemostatic abnormalities that range from thrombocytopenia, consumption coagulopathy to hemolysis, elevated liver enzymes, and low platelets (HELLP) are the most ominous complications seen. This study was taken to evaluate the nature of these special hematological abnormalities in PIH.

Materials and Methods: A total 200 patients with clinical diagnosis of PIH referred to the department of pathology for hematologic evaluation over a period of 1½ year were included in the study. Complete hemogram, routine urine examination, and aspartate aminotransferase/alanine aminotransferase were done in all patients. Coagulation tests such as prothrombin time activated partial thromboplastin time, thrombin time, and D-dimer were carried out only in patients with thrombocytopenia (platelet count <1.5 lakhs), i.e., on 42 patients.

Results: Around 112 patients were grouped as severe PIH and 88 patients were grouped as mild PIH. Five of the severe PIH patients and only one of the mild PIH patient progressed toward HELLP syndrome. Useful parameters in the hemogram were blood picture to indicate microangiopathic hemolytic anemia, consumption coagulopathy, reticulocytosis, and leukocytosis which helped to identify the need for early initiation of specific therapy. The D-dimer test along with the platelet count was useful in predicting impending disseminated intravascular coagulation. HELLP syndrome with its grave prognosis was identified in 6 patients using blood picture and elevated liver enzymes.

Conclusion: This study shows that repeated hemogram and study of blood smear can go a long way toward identifying patients who are likely to go in for one or the other complications of PIH and identify those requiring specific component therapy by undertaking coagulation studies in a certain percentage of these patients.

Key words: Coagulation, Hemolysis; elevated liver enzymes and low platelets, Pregnancy-induced hypertension, Thrombocytopenia

INTRODUCTION

Pregnancy-induced hypertension (PIH) is the most common disorder of pregnancy affecting approximately 5-7% of pregnancies and is a significant cause of maternal and fetal morbidity and mortality.[1] The incidence of PIH in India ranges from 5% to 15%.[2] The majority of patients remains in mild to moderate group and does not have any major obstetric problems. However, in a certain proportion of patients, the risk to the mother can be significant and includes the possible development of disseminated intravascular coagulation (DIC), intracranial hemorrhage, renal failure, retinal detachment, pulmonary edema, liver rupture, abruptio placentae, and death. However, in a certain percentage of patients, the disease can progress to a more severe form with maternal risk of convulsions, cerebrovascular accidents, or increasing morbidity. For the fetus, it is also associated with placental insufficiency, intrauterine growth retardation, and rarely even intrauterine device.[3]

Hemostatic abnormalities ranging from thrombocytopenia, consumption coagulopathy to the triad of hemolysis, elevated liver enzymes, and low platelets (HELLP) are

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the more ominous complications seen in severe PIH. Thrombocytopenia is the most common hemostatic abnormality and its detection is important as it is one of the preventable factors contributing to some cases of life threatening cerebral and hepatic hemorrhage.[4] In view of the magnitude of coagulation changes that occurs in normal pregnancy, it i not surprising that pregnant or puerperal patient develops overt thromboembolic or coagulation abnormalities. It is equally reasonable to explore whether more subtle coagulation fibrinolytic changes develop into patterns of pathologic significance in diseases unique to pregnancy like toxemia.[5]

Superimposed HELLP syndrome develops in 4-12% of women with pre-eclampsia or eclampsia.[6] HELLP syndrome is severe form of pre-eclampsia, which poses a significant threat to both mother and fetus. This acronym HELLP was first coined by Weinstein, in 1982, to emphasize the triad of hemolysis, elevated liver, and low platelets. Based on the lowest observed maternal platelet count, HELLP syndrome is classified into three classes: Class 1 - If platelet count <50,000/cumm, Class 2 - If platelet count is >50,000 and <100,000/cumm, and Class 3 - If platelet count >100,000 and <150,000/cumm.[7]

Pathophysiologially, it is characterized by microangiopathic hemolytic anemia associated with liver and kidney damage that can progress to DIC having fatal termination.[6]

This study was taken up to evaluate the nature of these hematological abnormalities in PIH. Evaluation of peripheral smear with a special reference to red blood cell morphology, platelet morphology, aggregation and number has been the important focus of the study. Abnormal and premature forms of erythrocytes can identify microangiopathic hemolytic anemia cases which can progress to levels which require aggressive therapy. Cases having platelet counts below 1.5 lakhs were selected for performing battery of coagulation tests. Special emphasis was laid on D-dimer testing which can be used as a sensitive screening and follow-up tool for pre-eclamptic coagulopathy helping to define a subset of patients with severe disease. The D-dimer testing has been preferred over the test for fibrin degradation products (FDPs) as it has been established as a more sensitive tool for fibrinolysis.

MATERIALS AND METHODS

This was a prospective study carried out over a period of 1½ years at the Department of Pathology, Karnataka Institute of Medical Sciences, Hubli, a major tertiary health center for Karnataka. The total cases attending the outpatient department (OPD) per year are 3.5 lakhs of which around 15,000 cases attend antenatal OPD. Average number of antenatal cases admitted for delivery is 7000 per year of which about 450 cases are diagnosed to be having PIH.

About 200 patients diagnosed with PIH admitted to antenatal ward of KIMS and referred to the pathology department for hematological studies over a period of 1½ year were evaluated. Patients with essential hypertension, malnutrition, sepsis, neoplastic diseases, chronic diseases, valvular heart diseases, and those on anticoagulants were excluded. Clinical examination, complete hemogram, bleeding time, urine examination, and liver function tests were done on all the patients (200 patients).

Coagulation tests of prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), and D-dimer were done only on patients with platelet count below 1.5 lakhs (42 patients).

After obtaining informed consent from all the patients, venous blood was collected using 21G disposable needle and disposable plastic syringe. 4 cc of blood was collected for complete hemogram, of which, 2 cc of blood was collected in ethylenediaminetetra-acetic acid bulb for determination of hemoglobin (Hb), red cell indices, packed cell volume, total count, and platelet count. This was determined using Sysmex K-1000 automated blood cell counter. The remaining 2 cc of blood was collected in a citrate bulb for estimation of erythrocyte sedimentation rate (ESR) by Westergren's method. One drop of blood was obtained by finger prick for preparing peripheral smear and stained by Wrights stain. Bleeding time was estimated by Ivy's method. In those cases, where coagulation tests were done an additional 1.8 cc of venous blood was collected in citrate bulb mixed with 0.2 ml of citrate and used for coagulation studies.

The reagent used for PT was liquiplastin (Tulip Diagnostics). Normal values using liquiplastin are between 10 and 14 s. For each lot of liquiplastin, the mean normal PT was established by taking plasma from 20 normal healthy individuals and obtaining the average of their PT values.

The reagent used for APTT was liquicelin (Tulip Diagnostics), and the normal value is 21-29 s. Controls were run simultaneously with each test using plasma from healthy individuals.

The reagent used for TT was Fibroscreen (Tulip Diagnostics). Normal values using this reagent are formation of solid gel clot in 5-15 s.

D-dimer was estimated using Tulip XL FDP. Quantification was done by preparing serial dilutions of plasma sample

using phosphate-buffered saline buffer solution − 1:2, 1:4, 1:8, 1:16, 1:32, and so on. Positive result was indicated by agglutination indicating a D-dimer level above 200 ng/ml. The absence of agglutination indicates a negative result. D-dimer levels in ng/ml were calculated using the formula:

$200 \times d$

Where, d = Highest dilution of plasma showing agglutination during quantitative test of the sample.

Statistical Analysis

Students *t*-test was used.

RESULTS

Of the 200 cases, 112 (56%) had severe PIH (diastolic blood pressure [BP] ≥110 mmHg) and 88 cases (44%) had mild PIH (diastolic BP ≤100 mmHg). Table 1 shows age distribution of PIH cases.

The mean age in mild PIH was 23.57 ± 3.76 and that in severe PIH was 23.49 ± 4.1. Of the 200 cases, 109 (54.5%) were primigravidas and 91 (45.5%) were multigravidas. Cases with mild PIH were asymptomatic, whereas all cases of severe PIH were symptomatic with headache being the predominant symptom present in 52 cases (46.43%) followed by epigastric pain in 21 (18.75%), blurring of vision in 8 (7.14%), reduced urine output in 6 (5.35%), vomiting in 8 (7.14%), and giddiness in 3 (2.68%) cases. Biochemical examination revealed 1+ proteinuria in 43 cases (48.86%) of mild PIH while majority (55 cases, 49.10%) of those with severe PIH had 3+ proteinuria. Serum bilirubin levels were raised in 1 case (1.14%) of mild PIH and 9 (8.04%) of severe PIH and was normal in the remaining cases. The mean serum bilirubin in the cases with HELLP was as shown in Table 2. The highest level of serum bilirubin of 13.5 mg/dl was seen in a case of HELLP, the range being 1.3-13.5 mg/dl.

Aspartate aminotransferase (AST) levels were slightly elevated (41-70 IU/L) in 3 cases (3.40%) of mild PIH and 28 cases (25%) of severe PIH. Mean AST in cases with HELLP was high as shown in Table 3. Alanine aminotransferase levels were markedly elevated (>70 IU/L) in 9 cases (8.04%) of severe PIH. Hb levels of all these 200 patients varied from 2.3 to 14.8 g%, the mean being 9.05 g%. ESR of these patients ranged from 5 to 170 mm/h. The mean corpuscular volume in mild PIH was 82.91 ± 10.35 and, in severe PIH, it was 81.21 ± 10.26. The mean corpuscular hemoglobin (MCH) in mild PIH was 23.83 ± 6.11 and, in severe PIH, it was 24.13 ± 4.63. The mean MCH concentration in mild PIH was 28.35 ± 5.21 and, in severe PIH, it was 29.30 ± 3.88. Total leukocyte count varied from 4000 to 43,000 cells/cumm. The reticulocyte count varied between 0.5% and 10%. It was raised (>2.5%) in 18 cases (20.45%) of mild PIH and 40 (35.71%) of severe PIH.

Platelet count was normal (>1.5 lakhs) in 81 cases (92.05%) of mild PIH and 77 (68.75%) of severe PIH. Platelet count was between 1 and 1.5 lakhs in 3 cases (3.40%) of mild PIH and in 10 (8.93%) of severe PIH. The count was between 50,000 and 1 lakh in 4 cases (4.55%) of mild PIH and 20 (17.86%) of severe PIH. Platelet count was below 50,000 in 5 cases (4.46%) of severe PIH, whereas in none of those with mild PIH. Bleeding time was prolonged (>6 min) in one case (1.14%) of mild PIH and 10 (8.93%) of severe PIH. 13 cases (11.60%) of severe PIH showed giant platelets in the peripheral smear. Table 4 shows the red cell morphology in mild and severe PIH.

Coagulation tests were done in only those who had platelet count below 1.5 lakhs/cumm, i.e. in 42 cases. 2 cases (28.57%) of mild PIH and 29 (82.86%) of severe PIH had prolonged PT (>14 s). The PT in severe PIH was significantly prolonged ($P < 0.05$). APTT was normal in all 7 cases of mild PIH and 27 cases of severe PIH but prolonged (>29 s) in 8 cases (22.86%) of severe PIH.

Table 1: Age distribution of PIH cases

Age group (years)	Number of cases (%)	
	Mild PIH	Severe PIH
15-20	13 (14.77)	16 (14.29)
20-25	34 (38.64)	51 (45.53)
25-30	35 (39.77)	35 (31.25)
30-35	04 (4.55)	06 (5.36)
35-40	02 (2.27)	04 (3.57)
Total	88 (100)	112 (100)

PIH: Pregnancy-induced hypertension

Table 2: Mean serum bilirubin levels in HELLP and non-HELLP cases

Patients groups	Mean±SD
HELLP	3.53±4.88
Non-HELLP	0.72±0.18

SD: Standard deviation, HELLP: Hemolysis, elevated liver enzymes, and low platelets

Table 3: Mean AST levels in HELLP and non-HELLP cases

Patients groups	Mean±SD
HELLP	253.83±196.33
Non-HELLP	34.35±16.09

SD: Standard deviation, HELLP: Hemolysis, elevated liver enzymes, and low platelets, AST: Aspartate aminotransferase

APTT was not significantly prolonged in severe PIH ($P > 0.05$). The TT was normal in 6 cases (85.7%) of mild PIH and 28 (80%) of severe PIH. TT was raised (>15 s) in 1 case (14.29%) of mild PIH and 7 (20%) of severe PIH. The TT in severe PIH was significantly prolonged ($P < 0.05$).

D-dimer levels in cases of mild and severe PIH are shown in Table 5. In the present study, HELLP syndrome was diagnosed in six patients based on the hematological parameters, blood smear examination, and liver function tests.

Table 4: Red cell morphology in mild and severe PIH cases

RBC morphology	Mild PIH	Severe PIH
	N (%)	*N* (%)
Normocytic normochromic	38 (43.18)	39 (34.82)
Dimorphic	16 (18.18)	24 (21.43)
Normocytic hypochromic	15 (17.05)	18 (16.07)
Microcytic hypochromic	13 (14.77)	17 (15.18)
Macrocytic	03 (3.40)	08 (7.15)
Microangiopathic hemolytic	01 (1.14)	05 (4.46)
Leukoerythroblastic	01 (1.14)	01 (0.89)
Megaloblastic	01 (1.14)	00 (0.0)
Total	88 (100)	112 (100)

RBC: Red blood cell, PIH: Pregnancy-induced hypertension

Table 5: D-dimer levels in mild and severe PIH

D-dimer (ng/ml)	Number of cases (%)	
	Mild PIH	Severe PIH
Undetectable	4 (57.14)	9 (25.71)
200	2 (28.50)	16 (45.71)
>200	1 (14.2)	10 (28.57)
Total	7 (100)	35 (100)

PIH: Pregnancy-induced hypertension

Table 6 shows hematological parameters, coagulation profile, liver enzymes, and outcome in 6 cases of HELLP syndrome. In this study, 2 cases belonged to Class 1 HELLP syndrome and they had prolonged PT and APTT with TT on the higher side and marked increase in D-dimer levels indicating a state of DIC. Remaining 4 cases belonged to Class 2 HELLP and none of them belonged to Class 3. Four cases with HELLP syndrome underwent cesarean section. One patient died after cesarean and all the 6 patients delivered low birth weight babies.

DISCUSSION

Women with severe pre-eclampsia develop a variety of hematologic aberrations which have an impact on the outcome of these patients so that aggressive therapy can be initiated to prevent maternal and neonatal morbidity and mortality. Simple investigations such as complete hemogram, urine examination, and liver enzymes were done on all the cases that can detect platelet abnormalities, red cell abnormality, and detect patients likely to progress to HELLP syndrome. Coagulation profile was done only on patients with thrombocytopenia which is an important parameter for detecting DIC.

Women at any age are said to be at a greater risk for PIH.[3] In the present study, the mean age in mild PIH was 23.57 ± 3.76 and, in severe PIH, it was 23.49 ± 4.1. Similar observation was made by O'Brien *et al.*, who reported a mean age of 21.5 ± 0.9 in mild PIH and 21.3 ± 1.4 in severe PIH.[8] PIH is mainly a disease of young primigravidas. This observation was made by various authors and also in the present study.[9] Epigastric pain was the predominant symptom seen in 50% of severe PIH patients with HELLP in this study, similar observation was made by Weinstein.[10]

Table 6: Hematological parameters, coagulation profile, liver enzymes, and outcome in 6 cases of HELLP syndrome

Tests	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Hb (g%)	3.4	4.3	3.6	6.1	3.9	3.5
Total leukocyte count	8200	20.000	15,000	26,000	9900	4000
ESR (mm/h)	110	105	120	85	66	112
Reticulocyte count (%)	2.5	6	8	6	8	8
Platelet count (lakhs/cumm)	0.80	0.92	0.90	0.88	0.28	0.40
Bleeding time (min)	6'48"	6'40"	3'40"	3'50"	7'45"	7'40"
PT (s)	13.6	14.6	16	16.8	16	16
APTT (s)	28	25	30	26	32	24
TT (s)	10	13.6	16.2	16	14.8	16
D-dimer (ng/ml)	200	200	400	400	600	800
Serum bilirubin (md/dl)	1.3	1.8	1.9	13.5	1.4	1.3
AST (IU/L)	90	518	380	265	120	90
ALT (IU/L)	48	488	246	376	98	48
Mode of delivery	Vaginal	Cesarean	Cesarean	Cesarean (patient died)	Cesarean	Vaginal
Birth weight (kg)	2.2	2.1	2.2	2.3	2.3	2.1

HELLP: Hemolysis, elevated liver enzymes, and low platelets, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, PT: Prothrombin time, APTT: Activated partial thromboplastin time, TT: Thrombin time, ESR: Erythrocyte sedimentation rate, Hb: Hemoglobin

Proteinuria is an important sign of pre-eclampsia and diagnosis of pre-eclampsia is doubtful in its absence. In our study, proteinuria was present in all the cases (100%) of mild and severe PIH. However, Jambhulkar *et al.* observed proteinuria in only 68% cases of mild PIH and 92% cases of severe PIH.[11]

Estimation of serum bilirubin is important as it not only forms important criteria for diagnosis of HELLP syndrome but also its rise signifies the severity of the condition. Entman *et al.* in their study reported mean bilirubin concentration in severe PIH to be significantly higher than that in mild PIH.[12] However, in our study, there was no significant difference in mean bilirubin concentration between the mild and severe PIH groups. Serum AST appears to be the dominant transaminase released into the peripheral circulation with severe pre-eclampsia and HELLP syndrome. In the present study, the mean AST was higher in HELLP cases compared to non-HELLP cases which was similar to the observation made by de Boer *et al.*[13]

The present study showed raised ESR in most of the patients (85%). This is explained by the fact that pregnancy is one of the physiological causes of raised ESR and infection was ruled out in all these patients. Patients with severe pre-eclampsia have a microangiopathic hemolytic anemia, but it is not known whether increased red cell turnover occurs with milder form of this syndrome. Although hemolytic peripheral blood picture was present in only six cases, 18 (20.45%) of mild PIH and 40 (35.71%) of severe PIH showed raised reticulocyte counts (>2.5%). The highest value recorded was 10% in severe PIH with microangiopathic hemolytic anemia. Thrombocytopenia is the most common hemostatic abnormality of pre-eclampsia seen in approximately 50% of patients with pre-eclampsia according to a recent study done by Donimath *et al.*[14] In the present study, 22.5% patients had thrombocytopenia. Thomas *et al.* in their study observed that 16% of their patients had thrombocytopenia. Kelton *et al.* in his study concluded that there is evidence of both *in vivo* and *in vitro* platelet functional defect as the patients had disproportionate prolongation of bleeding time. Thus, patients with pre-eclampsia can have a significant defect in platelet function as well as number. The bleeding time may be important for evaluation of pre-eclamptic patients and provide information about the risk of any surgical procedures. In the present study, only 5.5% of patients had prolonged bleeding time, whereas in the study by Kelton *et al.* 34.6% patients with PIH had prolonged bleeding time.[15]

Microangiopathic hemolytic anemia is present to some degree in all patients with HELLP syndrome. This diagnosis is confirmed by finding of burr cells, schistocytes, and polychromasia on peripheral smear.[6] In the present study, six cases revealed these findings. All these six cases had thrombocytopenia and elevated liver enzymes. Documentation of HELLP syndrome is essential as aggressive therapy is initiated to prevent neonatal morbidity and mortality.

It is impossible to say which part of the maternal pathology reflects the HELLP syndrome. The associated DIC is an important aggravating factor often leading to deterioration of maternal status. The diffuse organ system damage particularly in liver, lungs, kidney, and brain may be a direct consequence of DIC causing vessel wall damage and increased vascular permeability. Arterial and venous macro and microthrombosis producing tissue hypoxia and ischemic necrosis. Hence, coagulation test is important in these patients and can reduce maternal morbidity and mortality if delivery is expedited as soon as diagnosis of suspected DIC is made.[6,16]

The reported hematologic findings in toxemia of thrombocytopenia, hemolysis, increased platelet adhesiveness, and increased FDPs are indicators compatible with intravascular coagulation. In the present study, an attempt was made to determine if the clinical categories of toxemia of pregnancy could be related to the syndromes of DIC on the basis of plasma assays of PT, APTT, and D-dimer estimation. Leduc*et al.* in their study concluded that DIC occurs once severe thrombocytopenia is present. Hence, one needs to obtain a complete blood count with platelet count at admission followed by serial platelet counts. Evaluation of PT, APTT, and fibrinogen should be added only if platelet count is <1 lakh in pre-eclampsia. This also saves the cost.[17] In this study, coagulation studies were done in patients with platelet count below 1.5 lakhs and showed that the mean PT was significantly prolonged in cases with severe PIH. Similar observation was made by Thomas *et al.* The prolongation of PT reflects picture of utilization of clotting factors due to mild intravascular coagulation. There were no significant differences between the mean APTT of mild and severe PIH patients in this study. However, the mean APTT in severe PIH was significantly prolonged in the study by Thomas *et al.* and Jambhulkar *et al.*[5,11] Significant prolongation of PTT in severe PIH indicates consumption of coagulation factors, especially factor VIII. In the present study, absence of prolongation of APTT could not be explained. TT was significantly prolonged in our study and similar observation was made by Jambhulkar *et al.*[11] Prolonged TT is ascribed to low concentration of substrate for thrombin, i.e., hypofibrinogenemia.

Coagulation abnormalities are considered one of the more ominous maternal complications in pre-eclampsia.

Unfortunately, there is no sensitive, reliable cost-effective screening tool to detect this and usually a battery of tests such as platelet count, PT, APTT, fibrinogen, and FDP are performed. None of these consistently reflect coagulation abnormalities such as D-dimer test. Although detection of degradation products traditionally has been used to assess fibrin formation, most of these assays cannot actually distinguish whether the products origin is fibrin or fibrinogen and, therefore, not specific for coagulation. The dimeric fragments on the other hand being unique to the process of fibrin polymerization specifically reflects its formation and breakdown.[18] Hence, in the present study, D-dimer was done rather than FDP. D-dimer was detectable, and it was above 200 ng/ml in 1 case of mild PIH and 10 of severe PIH in our study. We observed that D-dimer positive women had greater risk of cesarean section, premature delivery, and low birth weight. Similar observation was made by Trofatter *et al.* in their study.

Testing for D-dimer may be useful in early screening and follow-up for coagulopathy in PIH and may also help to define the subset of patients with severe disease.[19] D-dimer was also a better indicator of DIC compared to all other tests and correlated well with the outcome of pregnancy in the present study.

CONCLUSION

This study gives an outline of the investigation to be done in cases of PIH which can alert the physician of the severity of the disease so that appropriate and timely management can be initiated. Further, it proves the importance of peripheral blood smear examination which is a very simple and cost-effective tool and can detect the red cell abnormalities and qualitative and quantitative abnormalities of platelets frequently seen in PIH. Coagulation tests can be added only once there is thrombocytopenia, as increased platelet consumption is an early feature of this disorder. This also reduces the expenses of investigations. The importance of liver enzymes is furthermore emphasized, especially in patients with thrombocytopenia to detect HELLP syndrome.

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