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RESEARCH ARTICLE

A comparative study on coagulation profile and neutrophil-lymphocyte ratio in pregnancy-induced hypertension

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ABSTRACT

Background: Hypertension is one of the common medical complications of pregnancy and contributes significantly to maternal and perinatal morbidity and mortality. It is associated with alteration of hematological profile, of which thrombocytopenia is the most common which may be accompanied by a clinically evident consumptive coagulopathy or may be the sole abnormality seen. White blood cells are positively associated with inflammation. In medicine, neutrophil-to-lymphocyte ratio (NLR) is used as a marker of subclinical inflammation. An elevated ratio of peripheral neutrophil to lymphocytes has been recognized as a poor prognostic indicator in various cancers. **Aims and Objectives:** The objectives were to study and compare coagulation profile and NLR in pregnancy-induced hypertensive (PIH) patients with matched controls and to correlate the above parameters in relation to the severity of pregnancy-induced hypertension. **Materials and Methods:** Investigations were carried out in 90 PIH patients, aged 20–35 years, and in 90 normal pregnant women who are anthropometrically matched controls. Statistical analysis was done using Student's *t*-test and one-way ANOVA test, SPSS software version 20. **Result:** A significant decline in total platelet count (TPC), increase in prothrombin time, activated partial thromboplastin time, bleeding time, and clotting time was seen in PIH as compared to normal pregnancy. NLR is also significantly raised in PIH compared to normal pregnancy. **Conclusion:** TPC and NLR estimation can be taken as an early and rapid procedure for screening preeclampsia cases at admission followed by serial platelet counts while monitoring coagulation indices.

KEY WORDS: Thrombocytopenia; Bleeding Time; Clotting Time; Prothrombin Time; Activated Partial Thromboplastin Time; Neutrophil-lymphocyte Ratio

INTRODUCTION

"A mother's joy begins when new life is stirring inside. When a tiny heartbeat is heard for the very first time, and a playful kick reminds her that she is never alone" - Maureen Hawkins.

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Hypertensive disorders complicate 5–10% of all pregnancies and together they form one member of the deadly triad, along with hemorrhage and infection that contribute greatly to the maternal morbidity and mortality rates. Pregnancy-induced hypertension is the most common medical disorder of pregnancy that often results in multi-organ failure. Pregnancy-induced hypertension is defined as hypertension that occurs in pregnancy for the first time after 20 weeks of gestation and disappears following delivery.[1] Eclampsia is the occurrence of convulsions or coma unrelated to other cerebral conditions with signs and symptoms of pre-eclampsia.[2] Women with PIH may develop a variety of hematological aberrations.[3] Faulty coagulation of blood can be a cause of hemorrhages.[4] Out

of all hematological changes that occur in pre-eclampsia and eclampsia, thrombocytopenia is the most common abnormality found. Diagnosis of complications of PIH depends on many signs and symptoms as well as laboratory tests.

The tumor microenvironment, and in particular, the inflammatory response play an important role in cancer development and progression and may be associated with systemic inflammation.[5,6] Measurable parameters in blood that reflect the systemic inflammatory response are elevated C-reactive protein (CRP), hypoalbuminemia, increased levels of some cytokines, and increased levels of leukocytes and their subtypes.[7,8] Biochemical markers of inflammatory response have been incorporated in prognostic scores for several types of cancer.[9]

Neutrophil-lymphocyte ratio (NLR) is a marker of systemic inflammation and endothelial dysfunction. In recent years, it has been reported that the individual components of differential white cell count, specially the neutrophil and lymphocyte counts, may have clinical utility in predicting disease. An elevated NLR has been shown to be a prognostic indicator in various malignancies. In the literature, many studies have been shown that NLR has predictive value in determining the prognosis of various diseases. However, little has been known about the predictive values of NLR in pregnancy complications.[10]

Early assessment of severity of pre-eclampsia and eclampsia is necessary to prevent complications such as HELLP syndrome and increased maternal and fetal morbidity and mortality. Hence, this study is undertaken to assess the severity of pre-eclampsia, eclampsia, and coagulopathy by a method that is rapid, cheaper, and easily available so that they will guide us for management before the patient goes into complications.

Thus, the present study will be undertaken to find the changes that occur in the coagulation parameters and neutrophil-lymphocyte ratio in pregnancy-induced hypertension as compared to that in normal pregnancy.

MATERIALS AND METHODS

The present study was carried out in their third trimester of pregnancy, OBG department, KIMS Hubli, including 180 subjects.

Source of Data

The coagulation profile and neutrophil-lymphocyte ratio will be determined among pre-eclampsia and eclampsia patients, who are admitted to the maternity ward and labor room of the Obstetrics and Gynecology department and in the control groups, having age and anthropometrically matched apparently healthy pregnant women.

1. Ninety of these normal pregnant women in their third trimester were taken as control.
2. Another ninety patients were included in the study group. These patients were diagnosed with pre-eclampsia and eclampsia.

The diagnostic criteria used to define pre-eclampsia were as follows:

1. More than 20 weeks of gestation with age group of 20–35 years.
2. Blood pressure of 140/90 mm Hg or greater when readings taken twice 6 h apart.
3. Proteinuria of 1+ or greater by dipstick method in two random samples when measured 6 h apart.

These Cases were Further Categorized into Three Different Categories

Group A - non-severe/mild pre-eclampsia: Systolic blood pressure between 140 and 160 mm Hg and diastolic blood pressure between 90 and 110 mm Hg Proteinuria up to 1+.

Group B - severe/moderate pre-eclampsia: Systolic blood pressure between >160 mm Hg Diastolic blood pressure >110 mm Hg proteinuria >1+.

Group C - eclampsia: Pre-eclampsia associated with seizures.

Inclusion Criteria

i. Pregnant women between 37 and 42 weeks of gestation with pre-eclampsia and eclampsia.
ii. Normotensive pregnant women between 37 and 42 weeks of gestation.

Exclusion Criteria

1. Pre-existing medical disorders - diabetes mellitus, renal disease, any coagulopathies, chronic hypertension, and thyroid disorder.
2. Smokers, alcoholics.
3. Multifetal gestation.
4. Placental abruption or previa.
5. Age group <20 years and >35 years.
6. Medication (except multivitamins, iron, and calcium) which affect the present study.

After considering inclusion and exclusion criteria, the study groups were selected. The importance of procedure was explained to the guardian and the subjects. Informed consent was obtained from the subjects. A questionnaire form designed for the purpose of the study was filled, which included name, age, gestational age, and family history. A thorough physical examination was carried out on each subject. For each patient and control, height and weight were measured.

Methods of Collection of Data

1. Details of the study protocol will be explained to the subjects.
2. Informed consent will be obtained.
3. Detailed history will be taken.
4. General physical, systemic, and obstetrical examination will be done.
5. Routine blood investigations and coagulation profile will be done.

Ethical clearance has been obtained from the ethical committee.

Coagulation Parameters Done Are

- Total platelet count (TPC) - direct automated hematology analyzer - SYSMEX- XP 100.
- Prothrombin time (PT) - ERBA XL 100.
- Activated partial thromboplastin time (aPTT) - automated analyzer.
- Bleeding time (BT) - Duke's method.
- Clotting time (CT) - Capillary tube method of wright.
- NLR ratio - calculated by absolute neutrophil count divided by absolute lymphocyte count.

Statistical Analysis

Statistical analysis was performed using the SPSS (statistical package for social sciences) software version 20, under the guidance of Biostatistician. The statistical analysis was done using Students *t*-test and one-way ANOVA test. $P < 0.05$ was considered as statistically significant.

RESULTS

The mean age and gestational age in mild pre-eclampsia, moderate pre-eclampsia, and eclampsia are decreased, whereas SBP and DBP are increased compared to matched controls as shown in Table 1. There is a reduction in TPC, prolonged PT, activated aPTT, clotting time (CT), BT, and raised neutrophil-lymphocyte ratio in PIH patients compared to controls as shown in Table 2. It is also observed that the TPC, CT, and activated aPTT showed significant difference among mild pre-eclampsia, moderate pre-eclampsia, and eclampsia as shown in Table 3.

DISCUSSION

The present study shows a reduction in TPC, prolonged PT, activated aPTT, CT, BT, and raised neutrophil-lymphocyte ratio in PIH patients compared to controls.

Pre-eclampsia is a multisystem disorder of unknown etiology, unique to pregnancy. Women with pre-eclampsia usually develop raised blood pressure and proteinuria, but the condition is also associated with abnormalities of the coagulation system, disturbed liver function, renal failure, and cerebral ischemia.[35] Eclampsia is often a serious and life-threatening condition. Compared to pre-eclampsia, it carries a much higher risk of death and serious morbidity for the woman and her baby.[36] It has been shown that hematological aberrations such as thrombocytopenia and reduction in some plasma clotting factors may develop in pre-eclampsia women. A transient mild thrombocytopenia is seen due to increased platelet consumption during pregnancy.[37] The cause for the decrease in platelet count is multifactorial and is related to hemodilution, increased platelet consumption, and increased platelet aggregation driven by increased levels of thromboxane A2.[38] Decrease platelet count is attributed to increased platelet activation, enhanced aggregation, and destruction which appears to be due to endothelial damage.[39,40] Other studies show that the platelet counts in the normal pregnant women were found to be in the normal range. In mild and severe toxemia, there was fall in platelet count. The lowering of platelet count was a feature of toxemia of pregnancy.[54] Similar studies document significant prolongation PT in preeclampsia as compared to normal pregnancy.[34] The low platelet level was attributed to immunologically mediated destruction, platelet aggregation, and consumption, whereas prolonged BT and PTT and increased level of fibrin degradation products were due to reduced synthesis of coagulation factors due to liver dysfunction.[42-45] During pregnancy, there is an increase in the concentration of clotting factors II, V, VII, VIII, IX, X, and XII. Plasma fibrinogen level is significantly increased. Plasma fibrinolytic activity is suppressed during pregnancy and labor. It returns to normal within 1 hour of delivery of the placenta. This is due to liberation of plasminogen inhibitor from the placenta. Due to the hypercoagulable state in pregnancy, the presence of any provocative factor can easily upset the normal balance culminating in disseminated intravascular coagulation (DIC). In PIH, due to endothelial injury, the delicate hemostatic mechanism is triggered, which

Table 1: Anthropometric data of study group and control group

Parameters	Mild pre-eclampsia	Moderate pre-eclampsia	Eclampsia	Control
Age (years)	23.96±1.38	23.98±1.42	23.19±2.25	25±3.3
Period of gestation (days)	272.16±6.17	265.06±4.47	250.6±6.45	271.70±11.30
SBP (mmHg)	142±3.42	157±19.97	175.93±6.61	110±10.4
DBP (mmHg)	92.93±2.66	104±10.2	112±10.6	76.6±8.70

SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Table 2: Comparison of coagulation parameters between controls and cases

Parameter	Mean±SD		*t*	*P*	Significance
	Controls (*n*=90)	Cases (*n*=90)			
TPC	2.17±0.48	1.17±0.20	−18.09	<0.05	HS
PT	13.23±0.94	15.41±1.13	14.50	<0.05	HS
aPTT	29.45±2.29	36.20±4.95	11.72	<0.05	HS
CT	4.67±0.57	5.98±1.13	8.92	<0.05	HS
BT	2.72±0.71	4.68±0.77	17.64	<0.05	HS
NLR	2.35±0.78	4.64±1.08	16.23	<0.05	HS

TPC: Total platelet count (lakh cells/μL), PT: Prothrombin time (seconds), aPTT: Activated partial thromboplastin time (seconds), NLR: Neutrophil-lymphocyte ratio, HS: Highly significant, SD: Standard deviation

Table 3: Comparison of coagulation profile and neutrophil-lymphocyte ratio between mild pre-eclampsia, moderate pre-eclampsia, and eclampsia

Parameters	Mean±SD			*P*	Significance
	Mild pre-eclampsia (*n*=30)	Moderate pre-eclampsia (*n*=30)	Eclampsia (*n*=30)		
TPL (lakh/μL)	1.35±0.18	1.14±0.12	1.00±0.09	0.001	HS
PT (s)	15.27±1.14	15.52±1.11	15.45±1.17	0.69	NS
aPTT (s)	34.09±5.71	37.21±4.74	37.29±3.62	0.01	S
CT (min)	5.15±0.75	6.07±0.75	6.72±1.22	0.001	HS
BT (min)	4.6±1.00	4.66±0.53	4.79±0.70	0.62	NS
NLR	4.41±0.91	4.60±1.02	4.91±0.85	0.19	NS

TPC: Total platelet count (lakh cells/μL), PT: Prothrombin time (seconds), aPTT: Activated partial thromboplastin time (seconds), NLR: Neutrophil-lymphocyte ratio, HS: Highly significant, NS: Non-significant, S: Significant, SD: Standard deviation, BT: Bleeding time

leads to coagulation failure. The coagulation parameters, especially aPTT and D-dimer, can be used to monitor the progression of gestational hypertension to pre-eclampsia.[46] It is documented that platelet count and aPTT have predictive value in detecting DIC.[47] Prolonged BT may be due to generalized vasoconstriction. Prolonged CT was due to further depression of fibrinolytic activity. The lower platelet count in pre-eclampsia is associated with abnormal activation of coagulation system and is believed to reflect increased platelet consumption.[48] Similar studies done by Bellar *et al*. showed the consistent increase in CT with an increase in the severity of disease.[49] Studies also document prolonged BT in pre-eclampsia compared to normal pregnancy.[51] However, a study done by Louis Weinstein documents that hematological parameters consisting of BT, CT, and PT were reported to be normal in 96%.[52,53]

Neutrophil-lymphocyte Ratio

Many recent studies have suggested that an elevated NLR is associated with poor survival of subjects with cancer. The mechanisms underlying the association of high NLR and poor outcome of cancer patients are poorly understood. One potential mechanism underlying the prognostic impact of NLR may be an association of high NLR with inflammation. Neutrophilia as an inflammatory response inhibits the immune system by suppressing the cytolytic activity of immune cells such as lymphocytes, activated T cells, and natural killer cells.[31,32] The importance of lymphocytes has been highlighted in several studies in which increasing infiltration of tumors with lymphocytes has been associated with better response to cytotoxic treatment and prognosis in cancer patients.[33-35] Inflammatory cytokines and chemokines can be produced by both the tumor and associated host cells such as leukocytes and contribute to malignant progression. An elevated NLR has been associated with an increase in the peritumoral infiltration of macrophages and an increase in interleukin (IL)-17. Others have reported an association between elevated markers of a systemic inflammatory response with elevated circulating concentrations of several cytokines (IL-1ra, IL-6, IL-7, IL-8, IL-9, IL-12, interferon γ, interferon γ–induced protein 10kDa, monocyte chemotactic protein 1, macrophage inflammatory protein 1β, and platelet-derived growth factor, subtype BB). Neutrophils and other cells such as macrophages have been reported to secrete tumor growth promoting factors, including vascular endothelial growth factor, hepatocyte growth factor, IL-6, IL-8, matrix metalloproteinases, and elastases, and thus likely contribute to a stimulating tumor microenvironment. Although a variety of cytokines are implicated in the systemic inflammatory response, IL-6 in particular acts to increase the synthesis of acute-phase proteins, including CRP, and to decrease albumin production in the liver, the two elements encompassed by the Glasgow Prognostic Score, which has been shown to be prognostic in several solid tumors. Serum concentrations of IL-6 have been shown to be increased in 13 different

cancer types and have been associated with tumor stage and adverse prognosis.[36] Similar studies done by Kurtoglu *et al*. findings showed that the measurement of NLR periodically may be useful to predict high-risk pregnancies in terms of preeclampsia.[54] Studies done by Lowsby *et al*. conclude that neutrophil-lymphocyte count ratio outperforms conventional markers of infection, it is insufficient in itself to guide clinical management of patients with suspected bloodstream infection, and it offers no advantage over lymphocyte count. However, it may offer some diagnostic utility when taken into account as part of the overall assessment.[55] In an emergency care setting, both lymphocytopenia and neutrophil-lymphocyte count ratio are better predictors of bacteremia than routine parameters such as CRP level, white blood cell count, and neutrophil count. Attention to these markers is easy to integrate in daily practice and without extra costs.[56]

Limitations and Future Scope of the Study

Sample size in the present study is less. Thus, broad spectrum and multicentric studies are strongly recommended in this regard.

CONCLUSION

Thus, from all the observations, it can be concluded that pregnancy-induced hypertension is common in primigravidae. As the severity of pregnancy increases, the gestational age decreases. Proteinuria, pathological edema, severe headache, blurring of vision, and right upper abdominal pain are more common in severe cases of pre-eclampsia and eclampsia. Mild pre-eclampsia does not reveal any significant changes in coagulation parameters and platelet count as compared to normal pregnant control. Severe pre-eclampsia and eclampsia are characterized by thrombocytopenia and coagulation abnormalities indicating intravascular coagulation. Syndrome of hemolysis, elevated liver enzymes, and low platelets is a complication of severe pre-eclampsia and eclampsia. Platelet counts and activated aPTT have predictive value in severe cases of pregnancy with these routine screening tests, and coagulation disorders of preeclampsia and eclampsia can be detected. The detection of coagulation will be helpful to an obstetrician in treating the patients who probably may go into DIC.

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