ORIGINAL RESEARCH

A Comparative Study of Coagulation Profile in Normal Pregnancy, Mild Preeclampsia, and Severe Preeclampsia Patients

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Abstract

Introduction: Disorders of hypertension complicate approximately 5–10% of all pregnancies. Preeclampsia is a severe health issue that needs to be treated, especially in developing countries where it is more common and its risk of having detrimental effects is higher. This study assessed the severity of preeclampsia and coagulopathy to aid in the management of both situations before patients experienced complications as it is well known that an underlying coagulation disorder increases the risk of bleeding complications.

Aim: The aim of this study was to compare coagulation profile in normal pregnancy, mild preeclampsia, and severe preeclampsia patients.

Results: Preeclampsia patients' platelet counts were found to be significantly lower, their bleeding times to be noticeably longer, and their D-dimers to be noticeably greater in the current study when they were contrasted with normotensive pregnant women.

Conclusion: The coagulation profile is a crucial tool in the early detection of coagulation failure and its therapy to prevent the situation from getting worse. For a definitive diagnosis and therapy of the coagulation failure in preeclampsia and eclampsia patients, the use of additional parameters such as thrombin time, euglobulin clot lysis time, fibrinogen levels, and fibrinopeptide A is also recommended.

Keywords: Acute fatty liver in pregnancy, Adverse pregnancy outcome, Coagulation profile in preeclampsia, Disseminated intravascular coagulation, Eclampsia, FFP, Hypertension pregnancy induced, LSCS, Preeclampsia, Preeclampsia profile blood test.

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Introduction

Issues with hypertension complicate 5–10% of pregnancies.[1] Preeclampsia is a severe health issue that needs to be treated, especially in developing countries where it is more common and its complications are more likely. The coagulation and fibrinolytic systems significantly change during a typical pregnancy, making pregnancy a hypercoagulable state. Most frequent anomaly identified in preeclampsia is thrombocytopenia, out of all hematological abnormalities.[2] Severe preeclampsia causes intravascular coagulation, which increases the risk of bleeding issues. Women with both nonsevere and severe preeclampsia may be at an increased risk of maternal mortality and morbidity due to diffused intravascular coagulation (DIC).[3]

The placenta separating during the third stage of labor poses a considerable hemostatic challenge to the mother. The mother is able to get through this hemostatic barrier because of physiological changes brought on by pregnancy.[4] When combined, the altered fibrinolysis and coagulation during pregnancy signify a hypercoagulable state. This study assessed the severity of preeclampsia and coagulopathy, which can help us manage these circumstances before patients experience complications given that an underlying coagulation issue increases the chance of bleeding problems.

During pregnancy, plasma plasminogen levels rise concurrently with increases in fibrinogen.[5] On the other hand, a pronounced reduction in the immediate availability of plasminogen activator in the blood is indicated by a substantially prolonged euglobulin clot lysis time, which essentially measures plasminogen activator activity.[6] If the stimulus to fibrinolysis is strong enough, tissue plasminogen activator levels stay normal during pregnancy, allowing the pregnant woman to create enough plasmin to eliminate unwanted fibrin clots from the bloodstream.[7] Because delivery is typically followed by an immediate increase in plasma fibrinolytic activity, it is suggested that the placenta is responsible for the decreased fibrinolytic activity that characterizes normal pregnancy.[8] Additionally, after delivery, fibrin degradation products typically increase significantly.

Hematological abnormalities indicative of intravascular coagulation and, less frequently, erythrocyte destruction may cause difficulties in preeclamptic people, especially eclamptic patients.[9] Some researchers believe that DIC is not only a defining hallmark of preeclampsia but also plays a key role in its etiology as a result of renewed attention in these modifications.

Maternal thrombocytopenia can actually be brought on by preeclampsia and eclampsia. The platelet count will progressively return to normal within a few days of delivery.[10] In both direct and indirect antiglobulin assays, it was discovered that preeclamptic

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women and their newborns had higher levels of platelet-bound and circulating bindable immunoglobulin. These findings were interpreted as a shift in platelet surface. The clinical significance of thrombocytopenia is that it highlights the severity of the illness process in addition to the visible coagulation dysfunction. In general, platelet count has an inverse relationship with maternal and fetal morbidity and mortality.[11] Increased liver enzyme levels make this clinical picture even more concerning.

Preeclamptic patients' lower platelet counts, higher mean platelet volumes, and higher plasma concentrations of β-thromboglobulin (β-TG) and platelet factor (PF) are all indications that platelet activation is important in the pathophysiology of preeclampsia.[12]

A plasma platelet-activating factor (PAF) has been linked to the etiology of platelet activation in (HUS) and thrombotic thrombocytopenic purpura. Preeclampsia may be caused by comparable causes.[13] The fact that PAF was present in 45.4% of preeclampsia patients suggests that it played a part in the pathogenetic mechanism of platelet activation in this condition.

Preeclampsia affects both the endothelium condition and the hemostatic system. Markers for platelet activation and vascular constriction include β-thromboglobulin, PF-4, and 11-dehydrothromboxane B2/creatinine (11-DTXB2/Cr).

A normal platelet count does not guarantee that there are no other clinically significant clotting abnormalities present, according to studies aiming at understanding what degree of thrombocytopenia signals a risk of abnormalities in other coagulation indices. There is growing evidence that the etiology of preeclampsia involves increased coagulation activity.[14] The preeclamptic patient may have considerable changes in the activity of numerous clotting factors. These modifications may have an effect on both the hemostatic and fibrinolytic systems. This state of hypercoagulability that is already present during a typical pregnancy is accentuated by preeclampsia and eclampsia.

It has been suggested that intrinsic pathway activation may be altered by preeclampsia. Preeclamptic individuals had accelerated prothrombin times, which were linked to alterations in fibrinogen and factors II, V, and XI.[15] Thus, the common pathway appears to be hypercoagulable in the preeclamptic patients. Fibrin is the final result of the coagulation cascade. The division of fibrinogen into its two molecules, D- and E-fragments, is facilitated by plasmin. Thrombin causes the release of fibrinopeptides A and B, and fibrin is ultimately broken down into the D-dimer. The fibrinogen degradation product (FDP) X, Y, D, and E are created when the protease plasmin cleaves fibrin. The increase in any of these compounds is thought to indicate the production of thrombin and the transformation of fibrinogen into fibrin. In preeclamptic individuals, tissue type plasminogen activator, which is made by endothelial cells, may be released as a result of endothelial injury and trigger the fibrinolytic system.[16]

Some believe that fibrinopeptide A levels are more accurate indicators of coagulopathy or rapid thrombosis.[17] Women with preeclampsia have significantly higher fibrinopeptide A concentration than the normal gravidas.

Materials and Methods

This study was conducted at the Department of Obstetrics and Gynaecology at Gandhi Medical College and Hospital, Hyderabad, during the period of November 2019 to May 2021. It was an observational comparative study and included a total of 100 patients. Fifty controls were well matched with the study population which included a total of 50 patients with nonsevere preeclampsia (25 patients) and severe preeclampsia (25 patients). Inclusion criteria for enrollment into the study included the following:

- Control group: This group includes pregnant women aged 20–35 years with normal blood pressure and absent proteinuria between 36 and 40 weeks.
- Study group: This group includes pregnant women aged 20–35 years diagnosed as preeclampsia between 36 and 40 weeks with the following:
  - Group A: This group includes nonsevere preeclampsia with BP 140/90 to 160/110 with proteinuria up to 1 and no signs of end-organ damage.
  - Group B: This group includes severe preeclampsia with BP > 160/110 and proteinuria >1 and with signs of end-organ damage.

Exclusion criteria included the following:

- Pre-existing medical disorders: Diabetes mellitus, bleeding disorders, renal diseases, chronic hypertension, thyroid disorders, severe anemia, and sepsis
- Smokers and alcoholics
- Twin gestation
- Abruptio placenta
- With intrauterine contraceptive device (IUD)/established DIC
- H/o autoimmune disorders, idiopathic thrombocytopenic purpura (ITP)
- H/o receiving drugs like aspirin and anticoagulants

Blood coagulation parameters such as bleeding time, platelet count, clotting time, prothrombin time, activated partial thromboplastin time (aPTT), and D-dimer were compared between the study population and the control group.

Ethical Clearance

The ethical clearance was taken from the institutional ethical committee.

Statistical Analysis

Descriptional statistics were applied to analyze the data. An independent sample *t*-test was used to check for differences in mean parameter values like platelet count, clotting time (CT), prothrombin time (PT), aPTT, and D-dimer between study and control groups. *P*-value <0.05 was set for statistical significance.

Data entry was done in an excel spreadsheet for a descriptive analysis. The *t*-test, Chi-square test, and ANOVA/Fischer test were used.

Results

In the present study, coagulation parameters were compared in between normal controls and patients with preeclampsia or severe eclampsia. The distribution of the patients as per gestational age is depicted in Table 1. There were 21 primi subjects in each group.

The coagulation profiles of patients were monitored. The coagulation parameters were compared between test and control groups as depicted in Table 2.

Patients were followed up for the mode of delivery. Table 3 depicts the mode of delivery in each group.

In NSPE group, the NVD rate was more compared to the LSCS rate. In SPE group, the LSCS rate was 60% compared to NVD, which is 40%. The LSCS rate was more in severe preeclampsia group, most common cause for LSCS being Doppler changes.

Table 1: The distribution of patients among the groups according to gestational age

Gestational age	*Normal pregnancy*	*Nonsevere preeclampsia*	*Severe preeclampsia*	*Total*	*Chi-square*	*p-value*
36 weeks	6 (6%)	3 (3%)	3 (3%)	12 (12%)	0	1
37 weeks	16 (16%)	8 (8%)	8 (8%)	32 (32%)		
38 weeks	14 (14%)	7 (7%)	7 (7%)	28 (28%)		
39 weeks	8 (4%)	4 (4%)	4 (4%)	16 (16%)		
40 weeks	6 (6%)	3 (3%)	3 (3%)	12 (12%)		
Total	50 (50%)	25 (25%)	25 (25%)	100 (100%)		

Table 2: The comparison of coagulation parameters between cases and controls

Parameter	*Group*	*N*	*Mean*	*Std. deviation*	*F-test*	*p-value*
Bleeding time	Normal pregnancy	50	147.78	25.053	304.306	<0.01
	Nonsevere preeclampsia	25	171.92	27.991		
	Severe preeclampsia	25	225.52	17.694		
Platelet count	Normal pregnancy	50	2.96	0.86213	83.48	<0.01
	Nonsevere preeclampsia	25	2.16	0.68799		
	Severe preeclampsia	25	1.28	0.45826		
Clotting time	Normal pregnancy	50	311.5	71.849	78.223	0.42
	Nonsevere preeclampsia	25	296.44	58.101		
	Severe preeclampsia	25	308.32	59.132		
Prothrombin time	Normal pregnancy	50	11.126	1.498	3.401	0.027
	Nonsevere preeclampsia	25	10.458	1.0034		
	Severe preeclampsia	25	10.44	1.0614		
aPTT	Normal pregnancy	50	29.342	4.1183	5.965	0.037
	Nonsevere preeclampsia	25	27.184	3.2812		
	Severe preeclampsia	25	26.592	2.6638		
D-dimers	Normal pregnancy	50	1252.18	158.694	65.882	<0.01
	Nonsevere preeclampsia	25	1621.36	336.575		
	Severe preeclampsia	25	2252.24	589.343		

Table 3: Distribution of mode of delivery among the groups

Mode of delivery	*Normal pregnancy*	*Nonsevere preeclampsia*	*Severe Preeclampsia*	*Total*	*Chi-square*	*p-value*
LSCS	12 (24%)	11 (44%)	15 (60%)	38 (38%)	9.67	<0.01
NVD	38 (76%)	14 (56%)	10 (40%)	62 (62%)		
Total	50	25	25	100 (100%)		

The most popular medication for treating eclampsia and preventing it in people with severe preeclampsia is magnesium sulphate ($MgSO_4$). Table 4 depicts the use of $MgSO_4$ in between the two groups.

No patients in control and non-severe pre-eclampsia (NSPE) group were given random donor platelets (RDP)/fresh frozen plasma (FFP) transfusions. In the SPE group, four patients (16%) were given FFP/RDP as a result of coagulation failure. In this study, four patients (16%) set into coagulation failure—DIC. They were managed with FFP/RDP transfusions, apart from Inj. $MgSO_4$ and antihypertensives and managed by the termination of pregnancy. Blood components were transfused only in patients in the SPE group. In this study, no maternal deaths were observed.

Discussion

Hypertensive disorders are among the commonest medical disorders during pregnancy and continue to be a major cause of maternal and perinatal morbidity and mortality.[18] Preeclampsia is an idiopathic multisystem disorder specific to human pregnancy

Table 4: Distribution of $MgSO_4$ among the groups

$MgSO_4$	*Normal pregnancy*	*Nonsevere preeclampsia*	*Severe preeclampsia*	*Total*	*Chi-square*	*p-value*
Yes	0	0	25 (100%)	25 (25%)	100	<0.01
No	50 (100%)	25 (100%)	0	75 (75%)		
Total	50 (100%)	25 (100%)	25 (100%)	100 (100%)		

and the puerperium. Hematological abnormalities such as thrombocytopenia and decrease in some plasma clotting factors may develop in preeclamptic women. Subtle changes consistent with disseminated intravascular coagulation are potentially serious. Thus, the coagulation testing should be common in these patients for evidence of DIC and hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome.[19]

In this study, the platelet count was estimated to be 2.9 lakhs/$mm^3 \pm 0.86$ in the control group, 2.16 lakhs/$mm^3 \pm 0.68$ in the NSPE group and 1.28 lakhs/$mm^3 \pm 0.45$ in the severe pre-eclampsia (SPE) group. This is supported by a study conducted by Mohapatra et al.[20] where platelets were found to be 2.38 lakhs/$mm^3 \pm 0.33$ in the control group, 2.23 lakhs/$mm^3 \pm 0.19$ in mild Pregnancy induced hypertension (PIH), 1.82 lakhs/$mm^3 \pm 0.45$ in preeclampsia and 1.21 lakhs/$mm^3 \pm 0.49$ in eclampsia. Bhamri, Shailja S.[18] revealed the mean platelet count of normal pregnancy and severe PIH were 2.33 and 1.5 lakhs/mm^3 with significant *p*-value <0.001. This indicated that there is an inverse relationship between the severity of PIH and platelet numbers. The mean platelet count decreased from control to severe preeclampsia group.

In our study, BT showed an increasing trend from normal control to severe preeclampsia patients but was within the normal range. This is also supported by another study done by Ivankovic et al., which reported the association of preeclampsia with thrombocytopenia and prolonged bleeding time.

In this study, aPTT was 29.34 ± 4.1 seconds in normal control, 27.18 ± 3.28 seconds in the NSPE group and 26.59 ± 2.66 seconds in the SPE group the *p*-value was 0.037. This is also comparable with a study conducted by Prieto et al.[21] where no correlation between the severity of preeclampsia and the levels of prothrombin time, partial thromboplastin time, or fibrinogen was established.

Out of the total study population, 4 (16%) from the severe preeclampsia group went into coagulation failure. They were treated with fresh-frozen plasma and platelet concentrates apart from Inj. $MgSO_4$ and antihypertensive followed by termination by delivery.

Conclusion

A key tool in the early diagnosis of coagulation failure and its treatment to stop the problem from getting worse is the coagulation profile. Thrombin time, euglobulin clot lysis time, fibrinogen levels, and fibrinopeptide A are a few more indicators that should be used for a conclusive diagnosis and treatment of coagulation failure in preeclampsia and eclampsia patients. Preeclampsia patients' platelet counts were found to be much lower, their bleeding times to be significantly longer, and their D-dimers to be significantly higher when compared to pregnant patients with normotensive blood pressure. These results and their association with the progression and severity of preeclampsia warrant further research with a large sample size and serial monitoring of coagulation parameters.

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