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# Immature Platelet Fraction as a Predictive Marker of Severity in Hypertensive Disease of Pregnancy: a Prospective Cross-Sectional Study

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## Abstract:

**Objective:** This study aimed to evaluate the role of immature platelet fractions (IPFs) and the degree of thrombocytopenia and their association with the severity of hypertensive disease of pregnancy.

**Material and Methods:** One-hundred-and-ten primigravida females between 20-30 years of age, with a singleton live pregnancy, who attended the ANC clinic at Mahila Chikitsalaya, at over 20 weeks of gestation, with hypertensive disease of pregnancy, from November 2019 to August 2021, were enrolled in the study. Blood samples were obtained from all subjects at a regular ANC visits and at the time of admission in hypertensive disease of pregnancy and samples were analyzed within 4 hours of collection using an automated hematology system. IPFs were quantified using an optical fluorescence method. The levels of thrombocytopenia and immature platelet fractions were statistically analyzed against the severity of the disease.

**Results:** The mean IPF was highest in females with eclampsia (18.12±3.59%), followed by severe pre-eclampsia (14.81±2.91%), mild preeclampsia (10.55±3.26%) and was smallest in females with gestational hypertension (10.08±0.91%). This increase in IPF with increasing severity of hypertensive disorder of pregnancy was found to be statistically significant (p-value<0.001). The mean platelet count was lowest in females with eclampsia (1.60±0.41 lac/mm$^3$, followed by severe pre-eclampsia (1.65±0.36 lac/mm$^3$), mild pre-eclampsia (1.90±0.47 lac/mm$^3$) and highest in females with gestational hypertension (2.57±0.25 lac/mm$^3$) (p-value<0.001).

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**Conclusion:** Higher IPFs had a negative correlation with lower platelet counts and was significantly correlated s with disease severity. Changes in IPF in HDP may occur before development of thrombocytopenia, thus providing an opportunity to plan preemptive management strategies to reduce fetomaternal morbidity and mortality.

**Keywords:** hypertensive disease of pregnancy, immature platelet fraction, severity

## Introduction

Importantly, more than half of the hypertension-related morbidities in pregnancy are preventable. Early identification, proper counseling regarding warning signs, the importance of follow-up visits, and early diagnosis of disease progression by healthcare providers are helpful in the prevention and management of maternal and neonatal complications[1].

About 2% of all pregnant women develop pre-eclampsia. The incidence has increased by about 25% during the last decade[2].

Hemostatic changes that occur during normal pregnancy are exacerbated in pregnancies with hypertensive disorders. Pregnant women with hypertensive disorders, especially pre-eclampsia, show alterations in platelet indices. Platelet activation plays an important role in procoagulation in pre-eclampsia[3].

In the normal process of thrombopoiesis, newly-released immature platelets are larger and more reactive than mature platelets and, importantly, contain ribonucleic acid (RNA) and are known as reticulated platelets. These can be identified with nucleic acid stains and more accurately, via some newer automated hematology analyzers that combine flow cytometry principles with impedance analysis[4].

The immature platelet fraction (IPF) is a measurement of the percentage of reticulated platelets in peripheral blood. It corresponds to the level of platelet production in the bone marrow. It increases when platelet production rises and decreases when production falls. It can be used to distinguish between the common causes of thrombopoiesis[5]. IPF has been suggested as a sensitive index for monitoring changes in platelet production and destruction[6].

The data regarding the role of immature platelet fractions in pregnant women with hypertension are limited in developing countries like India, where hypertensive disease of pregnancy plays an important role in fetomaternal morbidity.

Hence, the present study aimed to find out the role of immature platelet fractions in hypertensive pregnant women and assess whether the immature platelet fraction (IPF) could be a useful predictor of disease development or as a sign of worsening pre-eclampsia.

## Material and Methods

This Hospital based cross-sectional analytical study was conducted at the Department of Obstetrics and Gynaecology at one of the largest tertiary care centres in Northern India, from August 2019 to March 2021. Primigravida females aged 20-30 years, with singleton live pregnancy, attending the antenatal clinic with over 20 weeks of gestation with hypertensive disease of pregnancy were included in the study. A total of 110 hypertensive diseases of pregnancy were included in the study. Patients with chronic medical disorders, disorders of platelet function, chronic hypertension, infectious diseases and viral infections, haematological disorders like aplastic anaemia, megaloblastic anaemia and myelodysplastic disorder, any other malignancy and those on aspirin/heparin therapy were excluded from the study. Hypertensive disorders of pregnancy cases were classified into Gestational hypertension, mild preeclampsia, severe preeclampsia, and eclampsia.

After taking informed written consent, detailed history, and general and systemic examination were done. Blood samples were collected in tubes containing ethylene diamine tetraacetic acid (EDTA) vials. Samples were analysed at the Central laboratory within 4 hours of collection using an automated haematology system. IPF was quantified using the optical fluorescence method. The level of thrombocytopenia and immature platelet fraction was analysed with the severity of the disease. Data were arranged in Microsoft Excel version 2010, and statistically analysed by statistical package for the social science (SPSS) version 23.

Ethical clearance was obtained from Institutional Ethics Committee.

## Results

Table 1 shows a comparison of immature platelet fractions among the different subgroups of cases of hypertensive disease of pregnancy in our study.

The mean IPF was highest in females with eclampsia (18.12±3.59%), followed by severe pre-eclampsia (14.81±2.91%), mild pre-eclampsia (10.55±3.26%) and females with gestational hypertension (10.08±0.91%). This increase in IPF with increasing severity of hypertensive disorder of pregnancy was found to be statistically significant (p-value<0.001).

Table 2 shows a comparison of platelet counts (lac/$mm^3$) among the different subgroups of cases in our study.

The mean platelet count was lowest in females with eclampsia (1.60±0.41 lac/$mm^3$ ), followed by severe pre-eclampsia (1.65±0.36 lac/$mm^3$), mild pre-eclampsia (1.90±0.47 lac/$mm^3$) and was highest in females with gestational hypertension (2.57±0.25 lac/$mm^3$). This decline in platelet count with increasing severity of hypertensive disorder of pregnancy was found to be statistically significant (p-value<0.001).

As shown in Table 3, the receiver operating characteristic (ROC) curve analysis indicated that both IPF and platelet count were good indicators of eclampsia and severe pre-eclampsia. However, a higher area under the curve indicated that IPF (area under the curve (AUC)=0.879) was better than platelet count (AUC=0.709). As calculated using Youden's index, the optimal cut off value for IPF was >13.3%, i.e., IPF >13.3% identified eclampsia and severe pre-eclampsia with a sensitivity of 77.6% and specificity of 90.2%. Platelet count on the other hand had a good sensitivity (87.8%) but low specificity (50.8%) at the optimal cut off of <2.025 lac/dl.

Table 3 shows the correlations between IPF and platelet count in all HDP patients. IPF showed a moderate negative correlation with platelet count, i.e., as IPF increased

**Table 1** Comparison of immature platelet fractions (IPF)(%) among study subgroups (HDP)

| Group | N | IPF (mean±S.D.) | p-value |
|---|---|---|---|
| Gestational Hypertension | 9 | 10.08±0.91 | <0.001 (S) |
| Mild Pre-eclampsia | 52 | 10.55±3.26 | |
| Severe Pre-eclampsia | 33 | 14.81±2.91 | |
| Eclampsia | 16 | 18.12±3.59 | |

IPF=immature platelet fractions, HDP=hypertensive disorders of pregnancy, S.D.=standard deviation

**Table 2** Comparison of platelet counts (lac/$mm^3$) among study groups

| Group | N | platelet count (lac/$mm^3$) (mean±S.D.) | p-value |
|---|---|---|---|
| Gestational Hypertension | 9 | 2.57±0.25 | <0.001 (S) |
| Mild Pre-eclampsia | 52 | 1.90±0.47 | |
| Severe pre-eclampsia | 33 | 1.65±0.36 | |
| Eclampsia | 16 | 1.60±0.41 | |

**Table 3** ROC Curve analysis for IPF and platelet count for differentiating eclampsia and severe pre-eclampsia from mild pre-eclampsia and gestational hypertension

| | IPF | Platelet count |
|---|---|---|
| AUC (95% CI) | 0.879 (0.821–0.946) | 0.709 (0.613 – 0.805) |
| P-value | <0.001 (S) | <0.001 (S) |
| Critical cutoff | >13.3 | <2.025 |
| Sensitivity | 77.6% | 87.8% |
| Specificity | 90.2% | 50.8% |

ROC=receiver operating characteristic, IPF=immature platelet fractions, AUC=area under the curve

**Table 4** Correlations between IPF and platelet count in all HDP patients

| | |
|---|---|
| **r (Correlation coefficient)** | -0.416 (moderate negative correlation) |
| **p-value** | <0.001 (S) |

IPF=immature platelet fractions, HDP=hypertensive disorders of pregnancy

platelet count decreased moderately.

## Discussion

In our study, table 1 shows comparison of immature platelet fraction among different subgroups of cases. The mean IPF was highest in females with eclampsia (18.12 ±3.59%), followed by severe pre-eclampsia (14.81±2.91%), mild pre-eclampsia (10.55±3.26%) and minimum in females with gestational hypertension (10.08±0.91%). This increase in IPF with increasing severity of hypertensive disorder of pregnancy was found to be statistically significant (p-value<0.001).

Similarly, a cross -sectional study done by Moraes et al. (2015)[7], to evaluate the IPF in patients diagnosed with a gestational hypertensive disorder and found that the IPF in gestational hypertensive disorder were significantly higher than in normotensive pregnancy. (IPF: 3.8, 2.4–5.1%; 8.6, 5.8–10.6%; 7.3, 4.2–10.2%; p-value<0.001 for normotensive pregnancy, Pre-eclampsia syndrome, and non- proteinuric hypertensive pregnancy, respectively). They suggested that immature platelet fractions can be used as a sensitive index for monitoring changes in alteration in platelet production and destruction and could be used in daily routine as an additional tool in the management of pregnant women.

Also, those findings were in agreement with a retrospective monocentric study done by Bernstein and team[8] in 2019, data of 69 pregnant women between 20 and 42 weeks of gestation were analysed. Twenty-eight of them had preeclampsia, hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome or partial HELLP syndrome fitting the Tennessee criteria (study group 1). Furthermore, 41 normotensive pregnant women were included as controls (study group 2). In both groups the IPF was analysed and demonstrated that the values of IPF were significantly higher in patients with hypertensive diseases than in normotensives.

In our study, as shown in Table 2, the mean platelet count was lowest in females with eclampsia (1.60±0.41 lac/mm$^3$), followed by severe pre-eclampsia (1.65±0.36 lac/mm$^3$), mild pre-eclampsia (1.90±0.47 lac/mm$^3$) and gestational hypertension (2.57±0.25 lac/mm$^3$). This decline in platelet count with increasing severity of hypertensive disorder of pregnancy was found to be statistically significant (p-value<0.001). Our results were comparable with a study done by Mohapatra et al. (2007)[9] who found the platelet number 2.38 lacs/mm$^3$ ±0.33 in the control group, 2.23 lacs/mm$^3$ ±0.19 in their patients with mild pregnancy induced hypertension (PIH), 1.82 lacs/ mm$^3$ ±0.45 in their patients with pre-eclampsia and 1.21 lacs/mm$^3$ ±0.49 in their patients with eclampsia. These findings demonstrated an inverse relationship between the severity of PIH and platelet numbers. Sultana et al. (2015)[10] conducted a study on thrombocytopenia in pregnancy-induced hypertension in 100 cases, of which 2% were diagnosed with gestational

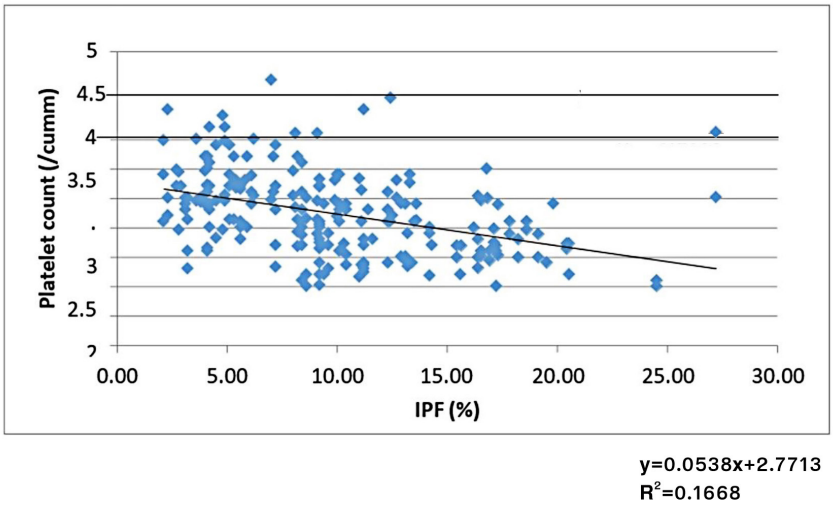


**Figure 1** Correlations of immature platelet fraction (IPF) and platelet count

hypertension, 56% with mild pre-eclampsia, 36% with severe pre-eclampsia, and 6% with eclampsia; their patients had varying platelet counts with 7.1% of the mild pre-eclampsia group having severe thrombocytopenia.

Another hospital-based study conducted by Meshram et al. (2014)[11] in 174 subjects found lower platelet counts in pre-eclampsia and eclampsia patients than in healthy pregnant controls. They correlated the severity of the pregnancy-induced parameters with the coagulation parameters and concluded that suspecting a deranged coagulation status early in the course of the disease helps to plan management strategies that have been proven to have a crucial role in reducing the morbidity and mortality of both mother and fetus.

In our study, as shown in Table 3, the ROC curve analysis indicated that both IPF and platelet count were good indicators of eclampsia and severe pre-eclampsia. However, a higher area under the curve indicated that IPF (AUC=0.879) was a better indicator than platelet count (AUC=0.709).

As calculated using Youden's index, the optimal cut-off value for IPF was >13.3%, i.e., IPF >13.3% identified eclampsia and severe pre-eclampsia with a sensitivity of 77.6%and specificity of 90.2%. Platelet count on the other hand had a good sensitivity (87.8%) but low specificity (50.8%) at the optimal cut off of <2.025 lac/dl.

The above study analysis is in agreement with the study done by Everett et al. (2014)[12], which found that an increase in IPF in patients with pre-eclampsia suggested increased thrombopoiesis in response to increased platelet consumption. They concluded that changes in IPF may be predictive of the development of thrombocytopenia in patients with pre-eclampsia.

As shown in Figure 1, in our study IPF had a moderate negative correlation with platelet count, i.e. as IPF increased, the platelet count decreased moderately, which was in concordance with a study done by Everett et al. (2014)[12], who did a case-control study to assess differences in thrombopoiesis in 10 women with uncomplicated normotensive pregnancy and 10 women who developed pre-eclampsia in the third trimester. They also observed that there was a negative correlation between higher IPF and lower platelet count in women with pre-eclampsia (r=-0.71, 95% confidence interval –0.92 to –0.15, p-value=0.02) but not in normotensive pregnant women.

**Limitations**

1. Further larger, longitudinal studies with serial measurements of IPF in hypertensive disorders of pregnancy (HDP) are needed for the results to be more significant.

2. A larger sample size is needed to determine the association between IPF and disease worsening.

## Conclusion

In our study, the immature platelet fraction was significantly higher in women with hypertensive disease of pregnancy compared with normal controls. Among women with a hypertensive disorder of pregnancy, immature platelet fraction was higher in women with pre-eclampsia and eclampsia than with gestational hypertension.

A higher immature platelet fraction had a negative correlation with lower platelet counts. It was significantly correlated with the severity of the disease. Also, changes in immature platelet fraction may occur before the development of thrombocytopenia in pre-eclampsia, eclampsia and HELLP.

Measurement of immature platelet fraction is a simple, cost-effective and new parameter for assessment of progression of disease in women with hypertensive disorder of pregnancy. It provides an opportunity for planning preemptive management strategies that can help in reducing morbidity and mortality of both mother and fetus.

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## Conflict of interest

The authors declare no conflicts of interest.

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