

A Cross-Sectional Study Investigating the Association of Serum Iron Concentration and Platelet Count as a Risk Biomarker among the Pregnancy-Induced Hypertensive Women in the Highlands Western Ghats of Nilgiris

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Abstract

Background: The elevated serum iron levels and reduced platelet count at 20–24th week of gestation period cause oxidative stress that leads to the pregnancy-induced hypertension (PIH). **Objectives:** The objective is to determine the prevalence of serum iron concentration, decrease in platelet count, and its association with PIH. **Methods:** A cross-sectional study was conducted in the secondary care hospital of Udhamandalam. A total of 150 study participants were enrolled. Descriptive analysis was performed for demographic characteristics. The Pearson Chi-square test was performed for categorical variables. To measure the strength of the association between the two variables, Pearson's correlation test and logistic regression analysis were performed. **Results:** The mean serum iron levels in both the groups were 99.01 ± 12.86 ug/dL and 82.76 ± 18.95 ug/dL, respectively, at a *P* value of 0.005. The platelet count (96.34 ± 9.77 vs. 116.68 ± 23.55) was significantly lower in PIH group. A moderate and weak correlation was seen between serum iron levels and systolic blood pressure (SBP) ($r = 0.435$; $P = 0.01$) and diastolic blood pressure (DBP) ($r = 0.435$; $P = 0.01$). Moderate negative correlation was observed between SBP, DBP, and platelet count. The risk of developing PIH is 6.76 times due to increased serum iron levels and 3.67 due to decreased platelet count. **Conclusion:** The serum iron levels were elevated, and the platelet indices were reduced in the PIH group. This should be considered a possible risk biomarker for PIH.

Keywords: Gestational hypertension, percent transferrin, platelet count, pregnancy-induced hypertension, serum ferritin, serum iron

INTRODUCTION

Pregnancy-induced hypertension (PIH) is one of the leading causes of maternal mortality and morbidity.^[1] During the gestation period of 20–24th weeks, serum iron levels are increased due to endothelial dysfunction and platelet activation which ultimately leads to oxidative stress.^[2] Iron is a transitional component; it is an impetus for the responses of Fenton and Haber–Weiss and can empower oxidative pressure and endothelial cell injury.^[3,4] The proposed mechanism is that, in feedback to endothelial injury, there is an activation of platelets, and it leads to release the contents of alpha granules such as serotonin and thromboxane, which ultimately results in vasoconstriction and activation of coagulation cascade. The secondary activation of this coagulation is combined with reduced fibrinolysis and impaired fibrin clearance that interferes with the microcirculation of organs.^[5,6]

The platelet indices in women with PIH are lower because of abnormal vascular response associated with increased systemic vascular resistance, enhanced platelet aggregation, activation and alteration of the coagulation system, and endothelial cell dysfunction. The decrease in the platelet count is probably due to consumption during low-grade intravascular coagulation.^[7]

However, elevated iron concentrations and reduced platelet count can be the product of clinical disorders in women who

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have already acquired the gestational hypertension. Few published studies are retrospective in nature and promoted us to conduct the prospective cross-sectional study to assess the relationship between the maternal serum iron concentrations, ferritin, and platelet count and the risk of developing the PIH.

MATERIALS AND METHODS

Study design and participants

The study was conducted at Government Head Quarters Hospital, Udhagamandalam, between July 2019 and August 2020. The study was approved by the Institutional Review Board, JSS College of Pharmacy, Ooty, (JSSCP/IRB/01/2019-20). A cross-sectional study was performed on nulliparous pregnant women of the maternal age of 18–35 years with 20–24th week of gestation period. The pregnant women were allocated into PIH and normotensive groups by randomization.

All the participants were allowed to take routine antenatal medication tablets folic acid 0.5 mg, ferrous sulfate 335 mg (100 mg of elemental iron), and calcium 1000 mg. Tablet labetalol 100 mg was used for pregnancy-induced hypertensive patients.

The pregnant women with the condition of chronic hypertension, kidney and liver diseases or active infection or known peptic ulcer, esophagitis, gastritis or hiatus hernia, and prepregnancy diabetes mellitus, immunological and inflammatory diseases, or thromboembolism were excluded from the study. Furthermore, pregnant women taking multivitamin tablets were not enrolled.

Data collection

A team of research staff visited the antenatal unit to screen the potential subjects. The pregnant women who fulfilled the eligibility criteria were invited to participate. The study participants were explained the objectives and procedures involved in the study. If the pregnant women agreed to participate in the study, a written, signed, and dated consent form in their native language was obtained.

A specially designed data collection form was used to collect the sociodemographic details, medical, medication history, supplement intake, obstetric details, concomitant medication consumption, anthropometric measurements, physical examination and vital parameters, and details of laboratory investigations.

Laboratory measurements

From each study participant, a 5 ml of venous blood was collected. All the hematological parameters, hemoglobin, red blood cell count (RBC), platelet count, total count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), MCH concentration (MCHC), and hematocrit were analyzed at Government Headquarters and Hospital, Udhagamandalam. Serum ferritin and percent transferrin saturation levels were analyzed at Thyrocare Laboratories, Mumbai, India. To measure the concentrations of

iron, the method of mass spectrometry with inductively coupled plasma was used. Serum ferritin levels were estimated using a fully automated bidirectionally interfaced chemiluminescent immunoassay. All the hematological parameters were estimated by fully automated hematology analyzer.

Main outcome variable

The primary outcome variables consist of serum iron concentration, platelet count, systolic blood pressure (SBP) maternal, diastolic blood pressure (DBP) maternal, serum ferritin, percent transferrin saturation, and secondary outcome variables included hemoglobin, RBC, hematocrit, MCV, MCH, leukocytes, WBC count, and aspartate aminotransferase (AST) level.

Statistical analysis

The sample size was calculated using GPower 3.0 software (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) by taking a reference from similar study objective to demonstrate the significant difference in means. To demonstrate a significant difference in serum iron and platelet count in PIH and normotensive groups, we considered determining sample size by fixing values of effect size (d), level of significance (α), and power ($1 - \beta$). For the values: $d = 0.60$, $\alpha = 0.05$, and 90% power, approximately 150 subjects were required in the study.

All analysis was conducted using the IBM SPSS statistical software (V.25.0; SPSS Inc., Chicago, Illinois, USA). Descriptive analysis was performed for demographic characteristics. Categorical variables were expressed as percentages and continuous variables as unadjusted means with standard deviations. Data were analyzed for normality before applying statistical tests. Independent sample t -test was performed for continuous variables, and Pearson Chi-square test was performed for categorical variables. A $P < 0.05$ was considered statistically significant. Based on the outcome of independent t -test, the data were further subjected to measure the strength of the association between the variables; thus, the Pearson's correlation test and logistic regression analysis were performed. To explain the relationship between one dependent binary variable and one or more independent variables, binary logistic regression analysis was performed.

RESULTS

Out of 191 pregnant women who were screened for eligibility criteria, 150 fulfilled the inclusion criteria. Figure 1 illustrates the details of screening, allocation, and analysis. Variables such as education ($P = 0.486$), occupation ($P = 0.257$), and consanguinity ($P = 0.702$) were equally distributed. However, factors such as diet and gravida showed a significant difference among PIH and normotensive groups [Table 1].

All the participants had an average SBP 146.40 ± 7.09 mmHg and 107.60 ± 11.72 mmHg ($P = 0.001$), DBP of 86.53 ± 9.65 mmHg, and 65.33 ± 6.00 mmHg ($P = 0.001$), respectively, in the PIH and normotensive group [Table 2].

The mean serum iron levels in both the groups were 99.01 ± 12.86 ug/dL and 82.76 ± 18.95 ug/dL, respectively,

at a $P = 0.005$. The mean cell volume value was 77.81 ± 5.30 and 77.31 ± 5.98 , respectively, and it was significantly different. The average serum ferritin (26.90 ± 6.13 vs. 34.16 ± 10.10), MCHC (32.74 ± 3.61 vs. 37.25 ± 2.59), and hematocrit (31.94 ± 3.09 vs. 36.85 ± 2.81) were significantly lower in the normotensive group in comparison with the PIH group at a significance of $P < 0.05$. However, average percent transferrin (28.50 ± 4.20 vs. 44.15 ± 3.88) and platelet count (96.34 ± 9.77 vs. 116.68 ± 23.55) were significantly lower in PIH group in comparison with normotensive group at $P < 0.05$ [Table 2].

The SBP ($r = 0.435$; $P = 0.01$) was also correlated with PIH which infers a positive moderate correlation between serum iron levels and SBP. DBP ($r = 0.24$; $P = 0.002$) was also correlated with serum iron which infers a positive weak correlation between serum iron levels and DBP. Moderate

positive correlation was observed between SBP and MCHC and ferritin, whereas weak positive correlation was observed between SBP and MCH. Moderate negative correlation was observed between SBP and platelet count and percent transferrin. There was no significant correlation between serum iron levels with AST levels which reflect that the raised iron levels cannot be explained by liver damage ($r = 0.12$, $P = 0.882$). Moderate positive correlation was observed between DBP and MCHC and ferritin, whereas weak positive correlation was observed between DBP and MCH total count. Moderate negative correlation was observed between DBP and platelet count and percent transferrin [Table 3].

The logistic regression model was statistically significant, $P < 0.001$. The model explained 23% (nagelkerke, r^2) of the variance in PIH and correctly classified 70.7% of cases. Increased serum iron will have 6.769 times more risk of having PIH when compared to normotensive mothers with 95% CI ranging from 3.184 to 14.389 which is statistically significant ($P = 0.001$).

The logistic regression model was statistically significant, $P < 0.001$. The model explained 11.3% (nagelkerke, r^2) of the variance in PIH and correctly classified 64.7% of cases. The decreased platelet count will have 3.357 times more risk of having PIH when compared to normotensive mothers with 95% CI ranging from 1.717 to 6.563, which is statistically significant ($P = 0.001$).

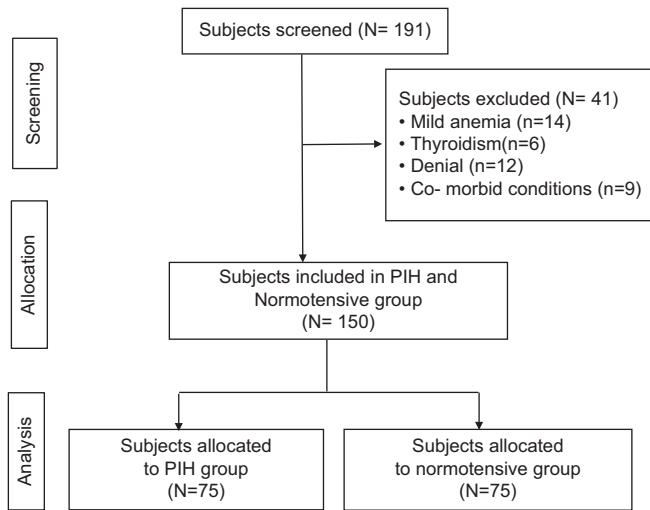


Figure 1: Flow chart of screening, allocation, and analysis

DISCUSSION

PIH is among the most critical complications. In this regard, the focus of the present study was on investigate the association between PIH and increased serum iron levels and decreased platelet count.

In the present study, there was no significant difference in the physical examination details between both the groups;

Table 1: Demographic characteristics of study participants at baseline visit

Characteristics	Categories	Total (N=150), n (%)	Normotensive group (N=75), n (%)	PIH group (N=75), n (%)	P
Education level	Primary	49 (32.7)	23 (30.7)	26 (34.7)	0.488
	Intermediate	69 (46)	38 (50.7)	31 (41.3)	
	Secondary	15 (10)	8 (10.7)	7 (9.3)	
	Undergraduate	17 (11.3)	6 (8)	11 (14.7)	
Occupation	Employed	23 (15.3)	9 (12)	14 (18.7)	0.256
	Housewife	127 (84.7)	66 (88)	61 (81.3)	
Consanguinity	Yes	114 (76)	58 (77.3)	56 (74.7)	0.702
	No	36 (24)	17 (22.7)	19 (25.3)	
Consanguinity degree	First degree	96 (64)	47 (62.7)	49 (65.3)	0.561
	Second degree	18 (12)	11 (14.7)	7 (9.3)	
	None	36 (24)	17 (22.7)	19 (25.3)	
Diet	Veg	69 (46)	51 (68)	24 (32)	0.001
	Nonveg	81 (54)	18 (24)	57 (76)	
Gravida	Single	71 (47.3)	29 (38.7)	46 (61.3)	0.034
	Multiple	79 (52.7)	42 (56)	33 (44)	

P: 0.05. Pearson’s Chi-square or Fisher’s exact test (for counts <5). PIH: Pregnancy-induced hypertension, N: Total number of subjects, n: Number of subjects in a given category, %: n/number of subjects with available results ×100, SD: Standard deviation

Table 2: The physical, vital sign examination, and hematological parameters details of the study participants in both the groups

Characteristics	Mean \pm SD			95% CI (upper-lower)	P
	Total participants (N=150)	Normotensive group (N=75)	PIH group (N=75)		
Physical and vital sign examination details					
Age (years)	24.31 \pm 3.59	24.32 \pm 3.37	25.21 \pm 3.72	-2.040-0.253	0.126
Gestation (week)	21.86 \pm 1.32	21.96 \pm 1.32	21.76 \pm 1.31	-0.226-0.626	0.356
Height (m)	1.51 \pm 0.057	1.518 \pm 0.055	1.512 \pm 0.06	-0.013-0.024	0.564
Weight (kg)	52.27 \pm 7.65	51.63 \pm 8.52	52.92 \pm 6.71	-3.76-1.84	0.304
BMI (kg/m ²)	22.81 \pm 3.48	22.44 \pm 3.88	23.179 \pm 3.00	-1.85-0.388	0.199
SBP (mmHg)	127 \pm 21.72	107.60 \pm 11.72	146.40 \pm 7.09	-41.92--35.67	0.001
DBP (mmHg)	75.93 \pm 13.31	65.33 \pm 6.00	86.53 \pm 9.65	-23.79--18.60	0.001
Details of hematological parameters					
Hemoglobin (g/dL)	12.33 \pm 1.18	12.197 \pm 1.107	12.47 \pm 1.251	-0.656-0.106	0.157
Total count (10 ³ cells/mm ³)	10.39 \pm 1.93	10.22 \pm 2.88	10.57 \pm 2.01	-0.983-0.265	0.258
Red blood cells (million cells per microliter (mcL))	4.107 \pm 1.774	4.066 \pm 0.508	4.148 \pm 0.246	-6.567-4.921	0.778
Hematocrit (%)	34.46 \pm 2.96	32.35 \pm 3.18	32.84 \pm 5.91	-2.02-1.04	0.530
Platelet count (10 ³ cells/mm ³)	106.51 \pm 20.66	116.68 \pm 23.55	96.34 \pm 9.77	14.51-26.15	0.001
MCV (fL)	77.56 \pm 5.64	77.31 \pm 5.98	77.81 \pm 5.30	-2.32-1.32	0.586
MCH (pg/cell)	30.03 \pm 3.60	29.00 \pm 3.17	31.05 \pm 3.74	-3.16--0.929	0.001
MCHC (g/dL)	35.99 \pm 3.30	32.74 \pm 3.61	37.25 \pm 2.59	-5.52--3.49	0.001
AST (units/L)	26.15 \pm 3.7	26.48 \pm 3.65	25.82 \pm 3.27	-0.46-1.77	0.251
Serum iron (mcg/dl)	90.88 \pm 18.08	82.76 \pm 18.95	99.01 \pm 12.86	-21.4--11.02	0.001
Ferritin (ng/ml)	30.53 \pm 9.09	26.90 \pm 6.13	34.16 \pm 10.10	-9.95--4.55	0.001
Percent transferrin (%)	36.32 \pm 8.82	44.15 \pm 3.88	28.50 \pm 4.20	14.34-16.95	0.001

P: 0.05 comparison of group means using independent sample *t*-test. PIH: Pregnancy-induced hypertension, N: Total number of subjects, SD: Standard deviation, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, CI: Confidence interval, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, AST: Aspartate aminotransferase

these findings are similar to studies conducted by Siddiqui *et al.*, Gutierrez-Aguirre *et al.*, and Serdar *et al.*^[8-10] In this study, the mean serum iron levels are higher in PIH group (99 \pm 12.86 Mcg/dl). The median serum iron levels were (1.7) higher in preeclampsia patients, in a study conducted by Siddiqui *et al.* In the study, conducted by Samuels *et al.*, it was found that the median serum ferritin was 6-fold higher in the preeclamptic patients and a correlation was observed between iron levels and serum ferritin levels ($r = 0.297$; $P = 0.024$).^[8,9,11,12] This increase is due to the endothelial dysfunction and platelet activation leading to oxidative stress.^[2]

In the present study, we found a decrease in the platelet count among the PIH group. In the study conducted by Alkholy *et al.*, the decrease in platelet count was seen in normotensive pregnant women (249,120 \pm 38,350/mm³). Whereas in the study conducted by Damani, there is an increase in the platelet count (158.7 \pm 68.4), this is because the platelet survival time is decreased, resulting in increased destruction of platelets.^[13,14] In the study conducted by Shetty *et al.*, the platelet count was found low, i.e., <100,000 in 42 subjects.^[15] This decrease in the platelet count is observed due to systemic resistance, leading to endothelial dysfunction.^[7]

The strength of the study includes that this study provides new insight into the pathophysiology of PIH. The limitation of the study includes serum iron levels and platelet count alone

cannot establish the diagnosis of PIH but should be used in conjunction with other clinical and laboratory studies to help with diagnoses of PIH. Thus, it is important for the physician to assess whether the cause-and-effect relation can be generalized.

CONCLUSION

The serum iron levels were elevated, and the platelet indices were reduced in the pregnancy-induced hypertensive group. The odds of developing PIH due to increased serum iron levels in pregnant women were found to be 6.76 times greater than the normotensive group. Similarly, the odds of developing PIH due to decreased platelet count in pregnant women were found to be 3.67 times greater than the normotensive.

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Table 3: Correlation between blood parameters with systolic blood pressure and diastolic blood pressure

Hematological parameters	Correlation coefficient (r)	95% CI (upper-lower)	P
SBP			
Serum iron (mcg/dl)	0.435	0.24-0.48	0.001
Platelet count (10 ³ cells/mm ³)	-0.515	1.68-2.0	0.001
Total count (10 ³ cells/mm ³)	0.067	-0.001-0.003	0.413
Hemoglobin (g/dl)	0.04	-2.16-3.78	0.591
Hematocrit (%)	0.564	2.43-3.94	0.001
MCV (fl)	0.060	-0.93-0.856	0.464
MCHC (g/dl)	0.517	2.125-3.686	0.001
MCH (pg/cell)	0.229	0.427-2.33	0.005
Ferritin (ng/ml)	0.348	0.468-1.196	0.001
Percent transferrin (%)	-0.809	-2.22--1.756	0.001
DBP			
Serum iron (mcg/dl)	0.249	0.068-0.299	0.002
Platelet count (10 ³ cells/mm ³)	-0.375	0.911-1.12	0.001
Total count (10 ³ cells/mm ³)	0.20	0.001-0.002	0.014
Hemoglobin (g/dl)	0.147	-0.152-3.45	0.072
Hematocrit (%)	0.612	1.62-2.56	0.001
MCV (fl)	0.003	-0.376-0.390	0.971
MCHC (g/dl)	0.462	1.096-2.087	0.001
MCH (pg/cell)	0.182	0.082-1.261	0.020
Ferritin (ng/ml)	0.365	0.313-0.756	0.001
Percent transferrin (%)	-0.708	-1.24--0.89	0.001

$P < 0.05$. Pearson 'correlation test. CI: Confidence interval, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Conflicts of interest

There are no conflicts of interest.

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