

Thrombocytopenia in Pregnancy: A Cross-Sectional Study in Northern Pakistan

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ABSTRACT

Objective: To determine the association of thrombocytopenia (mild, moderate & severe) with pregnancy-related disorders.

Study Design: Cross-sectional study.

Place and Duration of Study: Department of Haematology of Pakistan Railway Hospital, Rawalpindi Pakistan, in collaboration with the Departments of Obstetrics and Gynecology of Pak Emirates Military Hospital and Fuji Foundation Hospital, Rawalpindi Pakistan, from Oct 2018 to Oct 2019.

Methodology: Seventy-five pregnant females with platelet count $<150 \times 10^9/l$ were included. Blood samples were taken and analyzed for complete blood count, peripheral blood smear, manual count by Neubauer chamber, uric acid, urinary proteins, liver function tests (bilirubin & aspartate aminotransferase), lactate dehydrogenase, coagulation profile and viral serology (Hepatitis B & C).

Results: Out of a total of 75 thrombocytopenic pregnant females, gestational thrombocytopenia was most common (74.7%), followed by preeclampsia (17.3%), HELLP syndrome (4%), immune thrombocytopenic purpura (4%) respectively. Mild thrombocytopenia was frequently observed in patients of G.T. (62.5%), while moderate thrombocytopenia (84.6%) was generally detected in preeclampsia patients. Severe thrombocytopenia was mostly identified in patients with HELLP syndrome (66.7%) and immune thrombocytopenic purpura (66.7%).

Conclusion: Mild thrombocytopenia is mostly presented in gestational thrombocytopenia. Moderate thrombocytopenia was frequent in patients with preeclampsia, and severe thrombocytopenia was usually diagnosed in patients with HELLP syndrome and immune thrombocytopenic purpura, which require apposite and judicious management for the safety of mother and fetus.

Keywords: Gestational thrombocytopenia, HELLP syndrome, Immune thrombocytopenic purpura, Preeclampsia, Thrombocytopenia.

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INTRODUCTION

Thrombocytopenia is the most confronted haematological anomaly during pregnancy, besides anaemia.¹ Thrombocytopenia can be regarded as mild (platelet count of $100-150 \times 10^9/l$), moderate (platelet count of $50-100 \times 10^9/l$) and severe (platelet count $<50 \times 10^9/l$). There are various etiologies of thrombocytopenia, a few of which are unique to pregnancy. The most frequent is gestational thrombocytopenia which accounts for 75% of reported cases, then 15-20% of cases are related to hypertensive disorders (pre-eclampsia & HELLP syndrome), and 3% are due to an autoimmune process (immune thrombocytopenic purpura).²

Gestational thrombocytopenia (G.T.) is described as mild thrombocytopenia presenting with a platelet count of more than $70 \times 10^9/l$.³ In G.T., thrombocytopenia usually develops during late gestation and tends to resolve spontaneously after delivery. It is not

related to fetal thrombocytopenia and is generally a diagnosis of exclusion. Preeclampsia (P.E.C.) is the most frequent cause of isolated thrombocytopenia occurring in the late second or third trimester of pregnancy. P.E.C. accounts for 15%-50% of patients with low platelet count in pregnancy, and its severity correlates with the severity of thrombocytopenia.⁴ Platelet count usually declines before any other clinical manifestation of preeclampsia.⁵ Thrombocytopenia is the foremost and primary coagulation defect that occurs in all women with HELLP syndrome. The severity of thrombocytopenia is more in HELLP compared to preeclampsia. The American Society of Haematology defines 3 Immune thrombocytopenic purpura (I.T.P.) as isolated thrombocytopenia frequently occurring without recognizable and definite contributing factors.⁶ Manifestation of thrombocytopenia prior to pregnancy or its severity with a platelet count of $<50 \times 10^9/l$ escalates the probability of ITP.⁷ Diagnosis of I.T.P. in pregnancy does not necessitate bone marrow examination.⁸

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Very few studies available locally could signify the importance of thrombocytopenia in pregnancy-related disorders. Various existing studies,^{9,10} have researched a particular aetiology of thrombocytopenia in pregnant females. However, hardly any of them have related different etiologies with the severity of thrombocytopenia. Low platelet count is an early and useful marker for detecting the severity of pregnancy-related disorders for timely intervention and appropriate treatment to prevent the complications leading to maternal and fetal morbidity and mortality. Hence, this research was conducted to determine the severity of thrombocytopenia in various pregnancy-related disorders with low platelet count for accurate and timely management of mother and child.

METHODOLOGY

This cross-sectional study was conducted in the Department of Haematology of Pakistan Railway hospital Rawalpindi Pakistan in alliance with the Departments of Obstetrics and Gynaecology of Pak Emirates Military Hospital and Fauji Foundation hospital Rawalpindi Pakistan, after approval from the ethics review committee of Riphah International University Islamabad (Appl# Riphah/ERC/18/0311, 18th September 2018), from October 2018 to October 2019. Seventy-five pregnant females (18-40 years) with a platelet count of less than $150 \times 10^9/l$ were included. As the prevalence of thrombocytopenia in Pakistan is 5%,¹¹ the sample size was calculated by the formula: $N = Z^2 (pq) / E^2$, N =Desired sample size, Z = the standard normal deviation, usually set at 1.96, which corresponds to the 95% confidence interval, p =5% =estimated prevalence, $Q=1-p=95\%$, $E=5$ = margin of error.¹²

Inclusion Criteria: All the thrombocytopenic pregnant females were include in the study.

Exclusion Criteria: Patients having pseudo thrombocytopenia, microangiopathies other than HELLP syndrome (e.g., haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura), chronic diseases like diabetes mellitus, known hypertension, heart disease, renal disease, connective tissue disorders & chronic liver disease, infections, drugs (anti-inflammatory drugs, antibiotics antiepileptic, heparin, methyl dopa, digitalis and cyclosporine), megaloblastic anaemia and lymphoproliferative disorders were excluded from the study.

Samples of seventy-five thrombocytopenic pregnant females from Departments of Obstetrics and Gynecology in Pakistan Railway Hospital, MH and Fauji Foundation Rawalpindi Pakistan, were collected

using a non-purposive sampling technique. Platelet count of pregnant females was done by performing a complete blood count. Thrombocytopenia was confirmed by examining peripheral blood smear & by doing a manual count of platelets on the improved Neubauer chamber. In addition, the blood pressure of all the study patients was taken. Hypertensive patients were checked for increased urinary proteins, serum uric acid, serum bilirubin, aspartate aminotransferase (AST), lactate dehydrogenase (LDH) and reticulo-ocyte count. To calculate reticulocyte count, at least ten fields must be counted to calculate red blood cells per field, and the following formula are used for calculation: Number of reticulocytes in n fields= x , The average number of red cells per field= y , Total number of red cells in n fields = $n \times y$, Reticulocyte percentage = $[x \div (n \times y)] \times 100$.¹³

Pregnant females having elevated B.P. along with proteinuria were labelled as P.E.C. Those with elevated B.P. and raised L.D.H., bilirubin, A.S.T., and reticulocytosis were diagnosed with HELLP syndrome. Normotensive gravidas with a platelet count of $>70 \times 10^9/l$ & $<150 \times 10^9/l$ presenting in the third trimester were labelled as G.T. Normotensive females with platelet count $<100 \times 10^9/l$ had viral serology (hepatitis B and C) and coagulation profile (P.T. and APTT) done. If viral serology was negative & coagulation profile was normal, then they were considered to have I.T.P. Based on the tests mentioned earlier, all patients were distributed into the following four groups: Group A: G.T., Group B: P.E.C., Group C: HELLP syndrome and Group D: I.T.P.

About 5ml of venous blood was attained in a syringe after taking informed consent from all the pregnant females. Around 3 ml of blood was shifted in vacutainers containing EDTA for complete blood count, peripheral blood film analysis, manual count on improved Neubauer chamber and reticulocyte count (done in HELLP syndrome). A three-dimensional haematology auto analyzer SYSMEX XP-100i was used to measure platelet count. Quality assurance was done by running cell controls. Before analysis, samples were homogenized by placed on a mixer. Leishman stain was used to examine peripheral blood smear, and platelet count was assessed under an oil immersion lens. A peripheral blood smear was also analyzed for schistocytes (seen in HELLP syndrome), giant platelets (seen in I.T.P.) and platelet clumps (seen in pseudo thrombocytopenia). A 1:20 dilution of the whole blood sample was made for charging the improved Neu-

bauer chamber. Diluting fluid (1% ammonium oxalate) was used to lyse R.B.C. Platelet count was done in the central square of the Neubauer chamber (1 central and four corner squares) and calculated by using the following formula.¹⁴

Platelet count per liter=No of cells counted x dilution x 10⁶/Volume counted (ml).

The plain tube containing trisodium citrate (2ml of venous blood) was used for the coagulation profile (done in I.T.P. to exclude D.I.C.). The plain tube without anticoagulant (2 ml of venous blood) was used for biochemical tests (done in P.E.C. & HELLP syndrome). The biochemical tests were performed using Cobas c 111 semi-automated analyzers. Centrifugation at 5000 rpm for 5 min was done for biochemical analysis.

Statistical Package for Social Sciences (SPSS) version 21.0 was used for the data analysis. The chi-square test was applied when the sample size was >5 to find the association between different causes and severity of thrombocytopenia in groups of pregnant females. In addition, Fisher's exact test was applied when the sample size was <5. The *p*-value of <0.05 was considered statistically significant.

RESULTS

A total of seventy-five thrombocytopenic pregnant females were studied based on the study's inclusion criteria. Descriptive data of age, gestational age, platelet count and manual platelet count was shown in Table-I.

Table-I: Descriptive statistics of age (years), gestational age (weeks), platelet count (10⁹/l) & manual platelet count (10⁹/l).

	Maximum	Minimum	Mean ± SD
Age (Years)	23	40	29.9 ± 4
Gestational Age (Weeks)	11	38	31.8 ± 4.6
Platelet Count (10 ⁹ /l)	9	134	94.6 ± 27.7
Manual Platelet Count (10 ⁹ /l)	10	130	94.2 ± 24.3

G.T. was observed in 56 (74.7%) patients. Of these 56 patients, 35 (62.5%) patients had mild thrombocytopenia, while 21 (37.5%) had moderate thrombocytopenia. No patient had severe thrombocytopenia in G.T. Chi-square test was applied, and the *p*-value (0.001) was significant, showing an association of G.T. with thrombocytopenia. P.E.C. was diagnosed in 13 (17.3%) patients. Of these 13 patients, 2 (15.4%) patients had mild thrombocytopenia, while 11 (84.6%)

patients had moderate thrombocytopenia. There was no patient with severe thrombocytopenia in this group. *p*-value (0.007) was calculated using the chi-square test and was found to be significant. HELLP syndrome was present in 3 (4%) patients. Out of 3 patients, 1 (33.3%) had moderate thrombocytopenia while 2 (66.7%) patients had severe thrombocytopenia. No patient had mild thrombocytopenia in this group. The *p*-value was found to be significant with the value of 0.001 after applying the chi-square test. I.T.P. was diagnosed in 3 (4%) patients. Out of 3 patients, 1 (33.3%) had moderate thrombocytopenia while 2 (66.7%) patients had severe thrombocytopenia. *p*-value (0.001) was statistically significant in this group. Mild thrombocytopenia was mostly present in patients of G.T. In contrast, moderate thrombocytopenia was commonly present in patients of P.E.C. In contrast, severe thrombocytopenia was frequently present in patients with HELLP syndrome and I.T.P., as shown in the Table-II.

Table-II: Severity of thrombocytopenia in GT, PEC, HELLP syndrome and Immune thrombocytopenic purpura.

Study Groups	Thrombocytopenia			<i>p</i> -value
	Mild	Moderate	Severe	
GT (n=56)	35 (62.5%)	21 (37.5%)	-	0.001*
PEC (n=13)	2 (15.4%)	11 (84.6%)	-	0.007*
HELLP (n=3)	-	1 (33.3%)	2 (66.7%)	0.001*
IITP (n=3)	-	1 (33.3%)	2 (66.7%)	0.001*

(*Indicated statistically significant *p*-value)

DISCUSSION

Thrombocytopenia, second to anaemia, is the considerably frequent haematological disorder the pregnant woman faces.¹ Thrombocytopenia in pregnancy may result from several causes ranging from benign disorders such as incidental G.T. to life-threatening disorders such as HELLP syndrome associated with variable degrees of maternal and fetal morbidity and mortality. Therefore, careful analysis of the period of onset of thrombocytopenia, accompanying clinical manifestations, and precise lab testing is critical to provide appropriate diagnosis and proper maternal and fetal care in preparation for this haemostatic challenge.

In this study, the most common cause of thrombocytopenia in pregnancy was gestational thrombocytopenia, with a prevalence of 75%. These results were similar to studies by Ahmed *et al*, (2019) and Chandi *et al*, (2020) in Baghdad and India, which also stated that G.T. is most common in pregnant females.^{13,14} These 56 patients with G.T. had platelet counts >50 x 10⁹/l but <150 x 10⁹/l showing that there is no patient with

severe thrombocytopenia in this group. Of these 56 patients, 35 (62.5%) patients had mild thrombocytopenia, while 21 (37.5%) had moderate thrombocytopenia. This was comparable with the results of Ajibola *et al*, who also stated that mild thrombocytopenia is frequent in GT.¹²

According to the current study, the prevalence of P.E.C. was 17%. However, a much higher prevalence (33%) was reported by Sengodan *et al*, in their study carried out in India.¹⁵ Out of these 13 patients, 2 (15%) patients had mild thrombocytopenia while 11 (85%) patients had moderate thrombocytopenia. There was no patient with severe thrombocytopenia in this group of P.E.C. Contrasting findings were reported by Sultana *et al*, in their research in India.¹⁶ This might be due to the social, cultural and ethnic differences in the group of the population considered in other studies.

In this study frequency of HELLP syndrome was 4%. Out of 75 patients, three patients had HELLP syndrome. Out of 3 patients, 1 (33%) had moderate thrombocytopenia while 2 (67%) patients had severe thrombocytopenia. None had mild thrombocytopenia in this group. This was discordant with the findings of Rupakala *et al*. which showed 20% cases of mild thrombocytopenia, 60% cases of moderate thrombocytopenia, and 20% cases of severe thrombocytopenia.¹⁷ Socolov *et al*, in Romania also observed opposing results.¹⁸ The contrary findings reported in other studies might be because of racial and genetic differences.

In this study frequency of I.T.P. was 4%. Similar results were reported by a study conducted in Carolina.¹⁹ Wang *et al*, in China recognized an increased incidence of I.T.P., i.e., 28%.²⁰ In this study, out of 3 patients of I.T.P., moderate thrombocytopenia was detected in 1 patient (33%), while severe thrombocytopenia was observed in 2 patients (67%). Parallel findings were stated by Bum Jun Kim *et al*, and Wang *et al*, in their study.^{21,22} A cohort study in the U.K. also reported 42% cases of severe thrombocytopenia.²³ The much lower incidence of severe thrombocytopenia in the present study might be because of regional, cultural and climatic variations.

The disorders related to thrombocytopenia in pregnancy must be predicted promptly, appropriately, and precisely. In this manner, we can make a prior diagnosis of the preclinical sign of the various pregnancy-related pathologies, make a rapid diagnosis, and escape severe complications for the mother and fetus. Haematologists and obstetricians must be aware of

these alterations since variation from reference intervals may point to the beginning of complications. Even with its wide differential diagnosis, the cause of platelet disorders during pregnancy can be frequently determined with a detailed history, physical examination, and focused lab studies.

CONCLUSION

Mild thrombocytopenia was most common in gestational thrombocytopenia and can be managed by simple follow-up. Alternatively, moderate thrombocytopenia was usually observed in preeclampsia, and severe thrombocytopenia was frequently reported in HELLP syndrome and immune thrombocytopenic purpura, all of which require timely diagnosis and urgent management to save the mother as well as the fetus.

Conflict of Interest: None.

Author's Contribution

AE: Principal investigator, MW: SN: Data analysis, SS: Data collection, JU: Critical analysis, HI: Literature search.

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