BRIEF RESEARCH COMMUNICATION

Characterization of Thrombocytopenia in Pregnant Women at a Tertiary Care Center: A Preliminary Study of 121 Patients

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Abstract

Background: Partum-related hemorrhage is a major cause of maternal morbidity and mortality, the risk of which increases in women with thrombocytopenia. An accurate etiological diagnosis of thrombocytopenia in pregnancy is essential for optimal therapeutic management to prevent maternal and fetal morbidity and mortality. Our study aims to establish various prevalent causes of thrombocytopenia in pregnancy and its demographic characteristics.

Methods: In total, 121 pregnant patients visiting the Antenatal Outpatient Department and/or Emergency Department at a tertiary medical center with thrombocytopenia (platelet counts <1,50,000/μL) were recruited for the study. Detailed blood investigations were done to establish the accurate etiology of thrombocytopenia. Special attention was given to differentiating between pregnancy-associated causes and those incidental to pregnancy.

Results: Gestational thrombocytopenia (GT) accounted for 56.2% of the total cases, and hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome accounted for 13.2% of the cases, closely followed by idiopathic thrombocytopenic purpura (12.4%). Thrombocytopenia associated with nutritional deficiencies was seen in 5.8% of the cases. Other less common causes included fever-associated thrombocytopenia (2.5%), disseminated intravascular coagulation (DIC) (2.5%), acute fatty liver of pregnancy (AFLP) (0.8%), atypical hemolytic uremic syndrome (HUS) (0.8%), and anti phospholipid antibody (APLA) syndrome (0.8%).

Conclusions: Gestational thrombocytopenia (GT) is the commonest cause of thrombocytopenia during pregnancy.

Keywords: Gestational, Observational study, Pregnancy, Thrombocytopenia.

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Introduction

Thrombocytopenia is defined as a platelet count of <1,50,000/μL.[1] Thrombocytopenia can be classified as mild (platelet count of 1–1.5 lakh/μL), moderate (platelet count of 50,000–1 lakh/μL), and severe (platelet count of <50,000/–μL.[2] Thrombocytopenia during pregnancy develops in around 10% of gravidas.[3] Platelet abnormalities may precede pregnancy, develop during pregnancy coincidentally, or may be induced by pregnancy. Mean platelet counts in singleton uncomplicated pregnancies decreased progressively throughout the pregnancy and increased after delivery. Platelet counts in the first trimester were already significantly lower than that of the pre-pregnant state.

Multiple physiological as well as pathologic changes during pregnancy could contribute to this decline in platelet counts. Dilution of the blood caused as a result of a pregnancy-induced increase in plasma volume is an apparent cause, it causes a reduction of platelet count by around 10% of the pre-pregnancy values. In healthy nonpregnant women, up to one-third of the body's platelets are stored in splenic sinusoids. Pregnancy-related increase in splenic size may contribute to a further decrease in platelet count. Since placental circulation is also similar to splenic circulation, platelets may also accumulate within the placental intervillous spaces.[4] As multiple gestations will have larger, multiple placentae, this also explains the lower platelet count observed in multiple gestations as compared to singleton gestations.

Thrombocytopenia in pregnancy may also be a marker of underlying disorders that may be medical or pregnancy-associated.[5] Exclusion of GT and a search for an underlying disorder is prompted if the platelet counts fall below 50,000/μL.[6]

Spontaneous bleeding is the hallmark of thrombocytopenia. Although low platelet counts may lead to ultrastructural endothelial alterations, those alterations and the associated state of vascular fragility are unlikely sufficient to cause spontaneous rupture of the microvessel wall. For bleeding to occur, there must be endothelial injury as well as the presence of factors capable of damaging the basement membrane that will allow the escape of red blood cells in the extravascular space. Therefore, despite their misleading name, spontaneous bleeding events in thrombocytopenia are most likely

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Ethical approval: The study was approved by the Institutional Ethics Committee.

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Conflict of interest: None

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Table 1: Time of diagnosis

Gestational age at diagnosis	*No.*	*Percentage (%)*
Pre-conception	10	8.3
2nd trimester	7	5.8
3rd trimester	77	63.6
Intrapartum	27	22.3
Total	121	100.0

provoked and involve subclinical biological processes in which platelets normally intervene to ensure hemostasis.[7]

Methods

After obtaining permission from the Institutional Ethics Committee, the study was conducted at a tertiary institute over a period of 2 years. In total, 121 antenatal patients with thrombocytopenia (platelet count <1,50,000/μL) on their screening complete blood count (CBC) were recruited for the purpose of the study. On admission, a complete history was obtained and thorough examination was carried out. Additional biochemical investigations and special tests were carried out on the basis of the presenting complaints and examination findings.

- Inclusion Criteria:
  - All pregnant women above 18 years with platelet count <1,50,000/μL.
  - Pregnant woman who are willing to participate in the study.
- Exclusion Criteria:
  - Pregnancies complicated with fetal structural or chromosomal anomalies.
  - Preexisting maternal diseases like diabetes mellitus, cardiac, pulmonary, or renal diseases.

Based on their platelet counts, patients were grouped into three categories:

- Mild: platelet counts 1,00,000–1,50,000/μL.
- Moderate: platelet count 50,000–1,00,000/μL.
- Severe: platelet count <50,000/μL.

Patients were followed up until 1-week post delivery. Demographic characteristics of the patients, severity of the thrombocytopenia, and etiologic diagnosis along with special investigations required were recorded.

Results

Symptomatology

About 92.6% of patients who were asymptomatic for thrombocytopenia showed evidence only on CBC parameters. About 5% of patients had petechiae/purpura at presentation and 3.3% of patients presented with bleeding per vaginum.

Gestational Age at Diagnosis

Majority of the cases were diagnosed in the third trimester (63.6%). Table 1 shows time of diagnosis.

Severity

As gestational age progressed, there was an increase in the percentage of more severe degrees of thrombocytopenia. During the intrapartum period, 52.8% had mild thrombocytopenia, 38.84% had moderate thrombocytopenia, and in 8.26% of the cases, the thrombocytopenia was of a severe degree. There was an improvement in platelet counts post delivery by day 7 in 87.6% of the cases. Figure 1 shows distribution of severity of thrombocytopenia throughout the pregnancy.

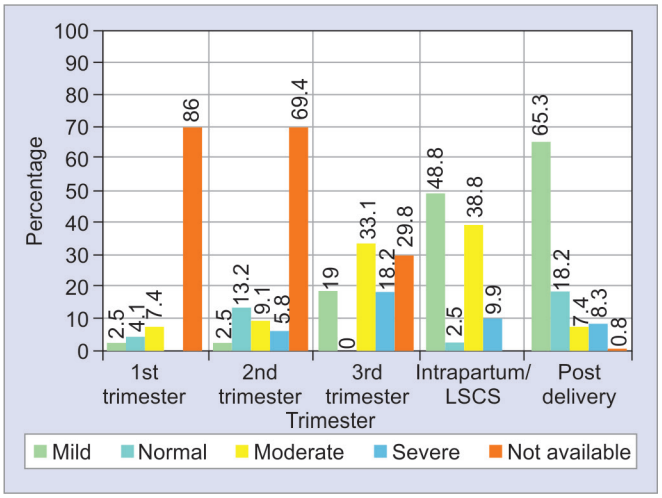

Fig. 1: Distribution of severity of thrombocytopenia throughout the pregnancy

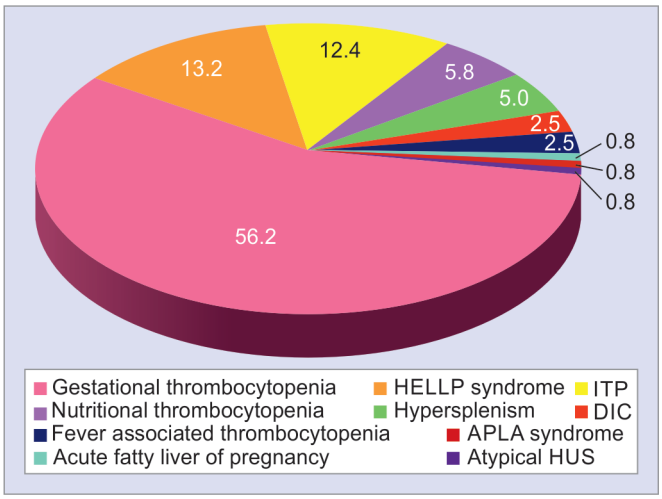

Fig. 2: Distribution of incidence of other causes

Diagnosis

Gestational thrombocytopenia (GT) was the commonest cause accounting for 56.2% of the total cases. The next most common cause found was HELLP syndrome (13.2%), closely followed by ITP (12.4%). Figure 2 shows distribution of incidence of other causes.

Specific Tests to Establish Diagnosis

Table 2 shows the various tests performed. Complete blood count (CBC) was performed in all the cases. Additional specific tests were done to establish diagnosis of thrombocytopenia in cases where specific etiology was strongly suspected or in cases of severe thrombocytopenia.

- A detailed DIC profile was obtained for 27 patients (with IUFD, massive hemorrhage, and hypertensive disorders) and was

Table 2: Various tests performed

Tests conducted	*No. of patients tested*	*Positive test results in*
DIC profile	27	5
Bone marrow biopsy	18	• 15 suggestive of ITP • 3 suggestive of megaloblastic anemia
PS for MP (*P. vivax*)	117	2
Leptospira IgM/IgG	117	0
Dengue NS1/IgM/IgG	117	4
APLA/LA	5	1
DsDNA	5	0
ANA	5	1

ANA, anti-nuclear antibody; APLA/LA, anti phospholipid antibody/lupus anticoagulant; DsDNA, double stranded deoxyribo nucleic acid

found to be deranged in five cases. In three cases, the low platelet count could be attributed to the DIC itself.

- Bone marrow biopsy was performed in 18 of the patients as per hematology consultation. BM biopsy picture suggestive of ITP was found in 15 patients, while 3 patients showed megaloblastic changes in the bone marrow.
- Screening for autoimmune diseases anti-nuclear antibody/double stranded deoxyribo nucleic acid/lupus anticoagulant (ANA/dsDNA/LA) was done as per hematology consultation. It was advised for five cases. Out of these, one tested positive for APLA/LA and ANA, while remaining four were negative for it. All the five cases tested were negative for anti-dsDNA.
- Fever profile was obtained for patients with thrombocytopenia where no obvious cause was identified. It included the following tests: peripheral smear for malarial parasite, Dengue NS1 antigen/Dengue IgG/IgM antibody, and Leptospira IgM/IgG antibody. Out of the 117 patients tested, 2 cases were positive for *Plasmodium vivax* on peripheral smear, while remaining 115 cases were negative. All the 117 tested patients were negative for leptospirosis. Dengue NS1/IgG/IgM positivity was found in 4 cases out of the 117 tested.

Age Distribution

The highest number of patients belonged to age-group 25–29 (36.4%) followed closely by the age-group 20–25 (35.5.%). About 20.7% were between the ages of 30 and 34 years and 7.4% were over the age of 35 years.

Parity Distribution

Primigravidae accounted for 38.3% and multigravidas for 56%. About 5.7% of the patients had bad obstetric history.

Associated High-risk Conditions

- *Medical high-risk conditions*: 4.1% patients had pancytopenia, 5% had coexisting liver disorders, 1.7% patients were COVID positive, 42.9% patients had anemia, and 6.6% patients had severe anemia. Two cases of malaria and four cases of dengue were found amongst our patients. Chronic hypertension, chronic ITP, heart disease, and HIV positivity were all found in one patient each.
- *Obstetric high-risk factors*: Eclampsia was the commonest occurring in 5% of the patients. Two patients each had placenta previa and pre-existing IUFD. One patient each had IUGR and twin gestation.

Potential Risk Factors

Potential risk factors for thrombocytopenia were identified in the patients studied, some of whom had multiple risk factors. About 32.2% of patients had pregnancy-associated hypertensive disorders which was the most common risk factor for developing thrombocytopenia in the current pregnancy. About 7.4% of patients had history of fever, 5.8% gave history of thrombocytopenia in previous pregnancy as well, and 2.5% of patients had history of recurrent pregnancy loss. No identifiable risk factor was found in case of 79 patients (65.2%) with thrombocytopenia.

Discussion

In our study, out of the total number of cases observed, 56.2% cases are GT, 16.5% cases are obstetric (hypertensive disorders, AFLP, obstetric DIC), and 27.3% are due to various medical causes. Amongst medical causes, thrombocytopenia as a result of ITP was seen in 12.4% cases and nutritional deficiency was seen in 5.8% cases. Fever-associated thrombocytopenia was observed in 2.5% cases.

Our findings are similar to that of Nisha et al.,[8] who observed that amongst the 150 cases that they studied, 64.2% were gestational thrombocytopenia, 22.1% were obstetric, and 13.68% were medical. Malaria-related thrombocytopenia was seen in 2.11% patients.

Just like our study, GT has been reported as the commonest cause of thrombocytopenia in pregnancy by systematic review and metanalysis of several studies conducted by Mohseni et al.[9]

In the study conducted by Chen et al.,[10] 63.5% cases were diagnosed as GT, 27.0% cases were ITP, 5.7% cases were blood system diseases (megaloblastic anemia, aplastic anemia, and myelodysplastic syndrome), and 3.8% cases were immune system disorders (systemic lupus erythematosus, antiphospholipid syndrome, and Evans syndrome), which is similar to distribution of various causes as observed by us.

In the Indian study conducted by Harde et al.,[11] the most common cause was found to be preeclampsia (33.3%) and preeclampsia with HELLP syndrome (20.7%), followed by GT (28%). Infectious causes (malaria, dengue, and leptospirosis) were found in 12.7%. Thrombocytopenia of moderate-to-severe range was found in preeclampsia, HELLP syndrome, and infectious etiology.

A study by Mbanya et al.[12] found that thrombocytopenic pregnant patients had a history of preeclampsia in 23.3% cases and malaria in 22.3% cases. Similar to these studies, we have also found that fever-related conditions are a significant cause for thrombocytopenia in pregnancy in tropical countries such as ours. Table 3 shows a comparison of various causes of thrombocytopenia.

About 92.6% of our patients were asymptomatic for thrombocytopenia. This is similar to the study conducted by Begam et al.[13] which reports 82.3% of the patients being asymptomatic for thrombocytopenia.

About 85.9% were diagnosed for the first time in third trimester (63.6%) or directly during labor (22.3%). This is similar to the observation conducted by Shamoon et al.,[14] where peak incidence of thrombocytopenia was in the third trimester. Most of the cases were diagnosed incidentally as platelet count is included in the routine CBC that is done for all pregnant patients late in pregnancy or when they report in labor. There is a lack of awareness amongst patients as well as physicians about the implications of these conditions. Poor antenatal follow-up and referral to tertiary care

Table 3: A comparison of various causes of thrombocytopenia

Causes	*GT*	*ITP*	*Immune disorders*	*HELLP syndrome*	*Fever related*	*Blood disorders*
Our study	56.2%	13.6%	0.8%	13.2%	3%	2.5%
Nisha et al.	64.23%	13.68%	22.1%	–	2.11%	–
Chen et al.	63.5%	43.5%	–	12.06%	–	5.7%
Harde et al.	42%	–	–	33.5%	12.7%	–
Mbanya et al.	–	–	–	22.3%	22.3%	–

center late in pregnancy or directly in labor also contribute. Lack of any specific symptoms until the thrombocytopenia reaches severe range also contributes to the late diagnosis.

As gestational age progressed, the severity of thrombocytopenia increased. Hence as the platelet count decreases in case of GT it is likely to fall below the threshold for diagnosis in later part of gestation. This is in accordance with the normal changes in platelet count during pregnancy that was illustrated by Reese et al.,[15] where it was shown that the decrease in platelet count started early, during the first trimester, and continued until delivery. This pattern was observed in all women with uncomplicated, singleton pregnancies. However, a platelet count of <1,50,000/μL was more likely amongst women with pregnancy-related complications such as diabetes mellitus, hypertension, etc. A similar platelet count fall was observed in the subgroup of women with pre-existing medical disorders associated with thrombocytopenia, such as ITP. Thus, even in women with ITP, lowering platelet counts during the advancing course of gestation may represent the normal, physiologic changes of pregnancy and not an exacerbation of the ITP.

Patients with platelet counts available in the first trimester included patients in whom the diagnosis had been established before the current pregnancy or detected to have ITP during this pregnancy. Patients diagnosed with thrombocytopenia in second trimester or early third trimester mainly included those with severe forms of hypertensive disorders of pregnancy which corresponds to the gestational age of onset of these disorders.[16]

Our findings are similar to those of Chen et al.,[10] who concluded that there was a significant difference in the onset time of thrombocytopenia between GT and ITP groups. Patients with ITP tended to have an onset in the first and second trimester, while those with GT tended to have a later onset of thrombocytopenia, mainly in the second and third trimester.

Conclusion

Majority of the cases are asymptomatic and diagnosed incidentally. There is a need for increased awareness amongst patients as well as clinicians to ensure earlier diagnosis and prompt management so as to prevent any adverse feto-maternal outcomes.

The diversity of factors resulting in thrombocytopenia indicates a wide variety of pathogeneses, the severity of which reflects the degree of thrombocytopenia as well as feto-maternal outcome.

Amongst the various etiologies, GT is the commonest. The thrombocytopenia is in the mild-to-moderate range, and platelet count recovers postnatally. A prior history of thrombocytopenia, underlying autoimmune disease or severe thrombocytopenia increases the chances of ITP being the underlying cause. However, it can be tough to differentiate ITP from GT in some cases of mild thrombocytopenia and no prior history of thrombocytopenia. In case of hypertensive disorders, the severity of thrombocytopenia usually correlates well to that of the underlying disease. It is difficult to differentiate hemolysis due to hypertensive disorders from hemolysis caused by rarer conditions such as Thrombotic Thrombocytopenia Purpura and atypical (HUS).[16] Hence a high index of suspicion must be kept for these conditions if the platelet count does not recover post-delivery.

In addition to these common etiologies, thrombocytopenia ensuing from endemic diseases (malaria, dengue) should be kept in mind as they have been found to be a significant risk factor for thrombocytopenia in pregnant patients in Indian subcontinent.

Another significant contributor is thrombocytopenia caused by nutritional deficiencies that are easily correctable.

Etiologies such as AFLP, DIC, thrombotic microangiopathies, though rare, contribute to significant maternal and fetal morbidity.

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