ORIGINAL ARTICLE

Thrombocytopenia during Pregnancy and Its Outcome – A Prospective Study

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Abstract:

Background: Thrombocytopenia is second to anemia as the most common hematological abnormality during pregnancy. Accurate etiological diagnosis is essential for optimal therapeutic management and thus can prevent maternal and fetal morbidity and mortality. *Aims and Objectives:* To determine various etiologies of maternal thrombocytopenia, their complications and fetomaternal outcome compared with normal pregnancy. *Material and Methods:* A prospective study was carried out in tertiary hospital, 1460 pregnant women who attended the Antenatal clinic regularly were enrolled. All were screened for thrombocytopenia in third trimester (after 28 weeks), women with normal platelet (n=1350) were taken in control group and those with low counts less than 150 $x10^9$/L (n=130) were included in study group. Etiology and fetomaternal outcome of thrombocytopenia in third trimester of pregnancy were evaluated and compared. *Results:* Gestational thrombocytopenia was the commonest etiology (68.46%). Incidence of thrombocytopenia due to severe preeclampsia and Hemolysis, Elevated Liver enzymes, Low Platelet (HELLP) syndrome in study group was 18.46% and 7.69% of them had medical cause like malarial or dengue fever. Major causes were Gestational Thrombocytopenia (GT), Idiopathic Thrombocytopenic Purpura (ITP), preeclampsia, HELLP syndrome, malaria, and dengue. Maternal complications due to bleeding tendencies like placental abruption, postpartum hemorrhage were evident in the study population. Fetal complications were significantly higher in study group. Early neonatal thrombocytopenia depended on etiology rather than severity of maternal thrombocytopenia. *Conclusions:* Outcome of pregnancy with moderate to severe thrombocytopenia depends mainly on the etiology of thrombocytopenia. Adverse outcomes are especially seen with pregnancy complicated by preeclampsia and HELLP syndrome. Fetomaternal outcome is favorable in gestational thrombocytopenia. Thus accurate etiological diagnosis is essential for optimal therapeutic management.

Keywords: Thrombocytopenia, Pregnancy, Gestational thrombocytopenia, Preeclampsia

Introduction:

Thrombocytopenia is second to anemia as the most common hematological abnormality during pregnancy [1]. Thrombocytopenia is defined as a platelet count below 150 $x10^9$/L, caused by accelerated platelet destruction or decreased production. It is classified as mild with a platelet count of 100–150x 10^9/L, moderate at 50–100 $x10^9$/L, and severe with less than 50x 10^9/L [2]. The prevalence of platelet count of less than 150x 10^9 /L in the third trimester of pregnancy is 6.6 to 11.6% [3-5]. A platelet count of less than 100 x 10^9/L is defined as thrombocytopenia by the international working group is observed in only 1% of pregnant women [6]. The normal range of platelets in non pregnant women is 150x10^9- 400 x 10^9/l.

Causes of thrombocytopenia during pregnancy [7] can be

1. Pre existing to pregnancy most common Idiopathic Thrombocytopenic Purpura (ITP).
2. Decreased platelet count or newly discovered thrombocytopenia in pregnancy which may or may not be related to pregnancy.
3. Acute onset of thrombocytopenia in cases of severe preeclampsia, Hemolysis, Elevated Liver enzymes, Low Platelet (HELLP) syndrome or Acute Fatty Liver of Pregnancy (AFLP).

Pregnancy is associated with a physiological fall in platelet count with leftward shift in distribution. It can result from various mechanisms like hemodilution and accelerated clearance. Incidental or gestational thrombocytopenia occurs in approximately 8% of all pregnancies and is the reason for 70 to 80% of cases of thrombocytopenia of pregnancy [3-5]. Although, the pathophysiology is not clear it may be because of increased activation, increased peripheral consumption and increased platelet aggregation driven by increase levels of thromboxane A_2 [8]. No confirmatory diagnostic test is available and it is the diagnosis of exclusion and occurs in mid second to third trimester.

Thrombocytopenia is typically asymptomatic, mild to moderate with two third women have platelet count 130 – 150 $x10^9$L and never less than 70 $x10^9$/L [3]. There is usually no past history of thrombocytopenia (except during previous pregnancy), resolves spontaneously within 1 -2 months of delivery and does not lead to thrombocytopenia in newborn but may recur in subsequent pregnancy [9]. The main competing diagnosis to gestational thrombocytopenia is ITP.

Pre-pregnancy thrombocytopenia and response to immune modulation with steroids and immunoglobulin favors ITP. Unfortunately, there are no laboratory tests to differentiate between the two conditions. ITP seen in 5% of cases of thrombocytopenia in pregnancy is characterized by a moderate to severe decrease in the platelet count, due to platelet auto-antibodies [10-12]. ITP patients with severe thrombocytopenia require treatment due to risk of maternal hemorrhage and also risk of neonatal thrombocytopenia.

Preeclampsia and HELLP syndrome is the second most frequent cause of thrombocytopenia in late second and third trimester, accounting for 21% of cases of thrombocytopenia at the time of delivery. It affects 5 to 8% of pregnant women and is defined with hypertension BP> 140/90 mm Hg, proteinuria (>0.3g in 24 hrs) after 20 weeks of gestation [13]. Coagulation abnormalities are rare if platelet count is more than 100 x 10^9/ L. Maternal platelet count return to normal within 3 to 5 days of delivery [10], it is responsible for maternal mortality and still birth as a result of placental abruption and preterm delivery [2]. AFLP is a rare but life threatening complication of third trimester of pregnancy (1 in 20,000 pregnancies) characterized by elevated liver enzymes, conjugated bilirubin > 5mg/dl and coagulopathy. AFLP with thrombocytopenia has overlapping features with HELLP [14].

Other etiologies of thrombocytopenia are rare, e.g. Thrombotic Thrombocytopenic purpura (TTP), Hemolytic Uremic Syndrome (HUS), Disseminated Intravascular Coagulopathy (DIC), Systemic Lupus Erythmatosus (SLE), Anti Phospholipids Antibody (APLA) and drug induced [2].

Basic laboratory evaluation of thrombocytopenia of pregnancy recommended is Complete Blood Count (CBC), reticulocyte count, blood smear, liver function test, viral screening (HIV, HCV, and HBV). Tests to be considered if clinically indicated are anti phospholipid antibodies, antinuclear antibodies, thyroid function test, *H. pylori* testing, DIC testing, VWB type testing, Direct coombs test [15-16]. Present study was carried out to determine various etiologies of maternal thrombocytopenia, their complications and fetomaternal outcome compared with normal pregnancy.

Material and Methods:

A prospective study was carried out in a tertiary hospital over a period of one year after taking approval from the Institutional Ethics Committee.

One thousand five hundred and sixty pregnant women who attended the ANC clinic regularly and were willing to deliver at our institute were included. They had platelet count estimation at the time of enrollment by automated blood count analyzer. All were screened for thrombocytopenia in third trimester (after 28 weeks), women with normal platelet were taken in control group and those with low counts less than 150x 10^9 /L were included in study group.

Detail history including maternal age, obstetric history, menstruation history, previous major illness, any medication history, past and present medical and surgical history was noted. General and systemic examination was done.

Pregnancy and labour complications if any, were noted as maturity of the fetus and mode of delivery, post partum hemorrhage, need for blood transfusion and platelet transfusion or operative intervention, and neonatal details in form of any morbidity and mortality was noted.

The detailed investigation in the form of blood test for Hb, TLC, DLC, bleeding time, clotting time, RFT, LFT, HBsAg and HIV were done in all cases of thrombocytopenia to ascertain the cause. Women with fever were tested for Dengue IgM, IgG and Malaria antigen. Coagulation tests (PT, APTT, FDP and fibrinogen) were done in those with signs or symptoms of DIC. Antiphospholipid antibodies were tested after ruling out all other etiologies. Women with moderate thrombocytopenia without any other etiology were classified as gestational thrombocytopenia.

Women with normal platelet count before 28 weeks had a repeat platelet count in the third trimester to detect gestational thrombocytopenia. All-thrombocytopenic cases were followed up till delivery. Platelet counts were repeated once in the postpartum period at 8 weeks. Neonates were screened for thrombocytopenia and any complications.

Data were complied in MS excel and analyzed in Statistical Package for Social Sciences (SPSS).

Results:

Out of the 1560 antenatal women attending ANC clinic, 1480 were included in the study after 28 weeks as 80 women had lost to follow up due to their personal reasons. Out of these 1480 antenatal cases, 130 were found to have thrombocytopenia with platelet count <150 x 10^9/L i.e prevalence of 8.78%. Of these, 78.4% were mild, 15.2 % were moderate and 6.4% were severe thrombocytopenia cases.

There was a statistically significant fall (P < 0.001) in the mean platelet count of the control group members from first trimester (212000 μl^{-1}) to third trimester (171,000 μl^{-10}) which may be due to physiological causes as none of them had thrombocytopenia. And no such change in the mean platelet count was seen with increasing period of gestation among thrombocytopenia cases.

Distribution of the cases according to their etiology is presented in following Table 1.

Table 1: Etiology of Thrombocytopenia in the Study Group

Etiology	n=130
Gestational thrombocytopenia	89(68.46)
Preeclampsia and HELLP syndrome	24(18.46)
DIC	2(1.53)
Hepatic diseases	1(0.76)
Malarial and dengue fever	10(7.69)
Megaloblastic anemia	2(1.53)
ITP	1(0.76)
APLA syndrome	1 (0.76)

Gestational thrombocytopenia (68.46%) was the commonest etiology. The prevalence of thrombocytopenia due to severe preeclampsia and HELLP syndrome in the study group was 18.46% and 7.69% of them had medical cause like malarial or dengue fever.

Both the cases of study and control group were followed till their delivery. The duration of pregnancy in both these group is represented in Table 2.

Thrombocytopenia per se do not affect mode of delivery. In the study group out of 130 cases 61.54% had vaginal delivery, 36.26% had Cesarean Section (CS) and 2.2% had instrumental delivery. All the cesarean sections were performed for obstetric/medical causes and none for thrombocytopenia. Whereas, in the control group 54% had normal vaginal delivery, 41% had CS and 5% had instrumental delivery as presented in Table 3.

Table 2: Duration of Pregnancy in Study and Control Groups

Duration of pregnancy	Study group (n=130)	Control group (n =1350)
Preterm	32 (25%)	170 (11%)
Term	98 (75%)	1180(89%)

Chi square test; P value =0.001 (significant)

Of the study group of 130 cases delivered during the study period, 74.3% delivered at term whereas 25.7% delivered preterm whereas in the control group the incidence of preterm delivery was only 11% of 32 patients who delivered preterm, 21 had induction of labour for maternal safety indication. Thus p value of 0.001 indicates that thrombocytopenia was significantly associated with preterm delivery.

Maternal complications seen in study group with thrombocytopenia like placental abruption (9.4%), postpartum haemorrhage (5.3%), episiotomy hematoma (2.5%), rectus sheath hematoma (1%) were more than in control group as only 3% cases had placental abruption and 1.3% had postpartum hemorrhage where as no one had episiotomy or rectus sheath hematoma. Also fetal complications were more in study group as represented in Table 4.

Table 3: Mode of Delivery in Study and Control Groups

Mode of delivery	Study group (n= 130)	Control group(n=1350)
Vaginal delivery	80 (61.54%)	729(54%)
Cesarean section	47(36.26%)	553(41%)
Instrumental delivery	03(2.2%)	68(5%)

Chi square test; p value = 0.153 (non significant)

Table 4: Maternal Complications and Fetal Outcome

	Control group (n=1330)	Study group (n=130)
Maternal Complication		
Placental abruption	3%	9.40%
Post partum haemorrhage	1.30%	5.30%
Episiotomy hematoma	0%	2.50%
CS incision site oozing (Rectus sheath hematoma)	0%	1%
Fetal outcome		
Still birth	1%	6%
Intrauterine growth restriction	8%	19%
Meconium stained liquor	4%	8%
Birth asphyxia	6%	13%
Neonatal thrombocytopenia	0%	7%

Out of 130 cases of thrombocytopenia 4 needed platelet transfusion for bleeding 3 with HELLP syndrome and 1 with DIC. A total of 15 (11.53%) women received blood transfusion in thrombocytopenia group versus 40 (3%) in non thrombocytopenia group.

A total of nine newborn had thrombocytopenia, out of which six were born to mothers with preeclampsia and HELLP syndrome, one to a mother with ITP, and two to mother with malaria . One neonate received platelet transfusion for Gastrointestinal (GI) bleeding.

Adverse pregnancy outcomes according to the etiology of thrombocytopenia are presented in Table 5. Intra Uterine Growth Restriction (IUGR) was more common in the preeclampsia and HELLP syndrome group compared with the other etiologies. Also placental abruption, stillbirths, and birth asphyxia was more in preeclampsia and HELLP syndrome group.

Out of 89 women with gestational thrombocytopenia, 77 had normal platelet count at 8 weeks post delivery, eight women had platelet count still below $150x10^9$ /l but had no complaints and 4 women were lost to follow up.

Table 5: Adverse Pregnancy Outcomes according to Etiology of Thrombocytopenia in Study Group

Adverse outcome	Etiology of Thrombocytopenia			
	GT	ITP	Preeclampsia HELLP	Malaria
IUGR	7	1	9	4
Placental Abruption	1	0	6	1
Still birth	0	0	4	1
Birth asphyxia	1	1	3	0

Discussion:

The present study was aimed at evaluating causes of thrombocytopenia in pregnancy and its fetomaternal effects.

Tejashwini *et al*. (2015) [17] conducted a study which demonstrated that platelet count was significantly decreased during pregnancy as compared to puerperium in the same woman due to haemodilution and increased platelet destruction. There was a physiologically increased fibrinolysis within the uteroplacental circulation in order to maintain blood flow. Stirling *et al*. (1984) [18], Wallenburg *et al*. (1978) [19], Douglas *et al*. (1982) [20], Fitzgerald *et al*. (1987) [21] these studies demonstrated that, thrombocytopenia is the most common haemostatic abnormality observed in pregnancy, in many healthy women (around 10%) late pregnancy was associated with thrombocytopenia. At least in part this was due to haemodilution but the increase in mean platelet volume suggests that a compensated state of progressive platelet destruction occurs. Additional evidence of *in vivo* platelet activation in late pregnancy was the increased concentration of b-thromboglobulin42 and of thromboxaneA2 derivatives. Usha Perepu and Lori Rosenstein (2013) [22] found that although thrombocytopenia during pregnancy was common, it was not frequently severe. This was consistent with our study results.

Burrows and Kelton 1993 [3] found thrombocytopenia in 6% and Sainio *et al*. [5] reported a 7.3% prevalence of thrombocytopenia in a population based surveillance study. In the present study, incidence of thrombocytopenia during pregnancy was 8.78%.Thus, the prevalence of thrombocytopenia in Indian population is similar to world literature (5–12%).In our study most cases of thrombocytopenia were due to gestational thrombocytopenia followed by other causes as preeclampsia and HELLP syndrome. Other causes were febrile conditions like malaria and dengue which are endemic in our area; some rare causes include DIC, ITP and APLA syndrome.

The major findings of our study were that increase complications, both maternal and neonatal such as placental abruption, preterm deliveries, birth asphyxia, IUGR, and stillbirths were seen in thrombocytopenia group.

Higher rates of preterm deliveries (< 37 weeks) were observed among thrombocytopenia group,

as management of preeclampsia and HELLP syndrome is early delivery of fetus. Labour induction could be a confounder for this association as 21 patients out of 35 with preterm delivery had to be induced for maternal indication. All fetal complications were significantly higher in study group like they were more due to maternal etiology like preeclampsia, HELLP syndrome and malaria (Table 4). Neonates may be at increased risk for thrombocytopenia. In Burrow (1993) study of women with thrombocytopenia, 216 had preeclampsia and HELLP and four gave birth to infants with severe thrombocytopenia [3]. Early neonatal thrombocytopenia was present in 7% of study group in present study, which is slightly higher than figure quoted by Parnas *et al*. (2006) [23] 7/199 (3.51%) neonates had moderate to severe thrombocytopenia.

Conclusion:

In our study we concluded that early inter-disciplinary evaluation of thrombocytopenia in pregnancy is required for optimal care of mother and the neonate as risk varies greatly depending on cause of thrombocytopenia. The common causes of thrombocytopenia in pregnancy are gestational thrombocytopenia, preeclampsia, HELLP syndrome, malaria and dengue. Gestational thrombocytopenia is associated with better maternal and perinatal outcome as compared to pre eclampsia, HELLP syndrome, ITP which expose them to life threatening complications as placental abruption, post partum hemorrhage, birth asphyxia and stillbirth. Thus accurate etiological diagnosis is essential for optimal therapeutic management.

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