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Original Research Article

Risk factors of thrombocytopenia in pregnancy

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ABSTRACT

Background: Thrombocytopenia in pregnancy occurs due to several etiologies which include both pregnancy specific and non pregnancy related causes. It is second only to anemia as the most common hematological abnormality encountered in pregnancy. Better antenatal care has led to increased detection. Once diagnosed, it is important to further evaluate and to determine the cause to optimize management. Several studies have been undertaken across the world; however there are very few studies in Kerala hence this study. The aim of this study was to determine the risk factors of thrombocytopenia in pregnancy.

Methods: This was a case control study undertaken in the Department of Obstetrics and Gynecology, Medical college Hospital, Trivandrum, Kerala. Using purposive sampling, a sample size of 96 cases and 96 controls were included in this study. "Cases" were antenatal women with thrombocytopenia and "controls" were consecutive women without it. Study period was 18 months and analysis was done using SPSS version 22.

Results: In 49% of subjects, the cause was identified as gestational thrombocytopenia, 39.5% cases were due to hypertensive disorders of pregnancy, 10.4% was due to ITP. SLE, AFLP, Dengue infection, HUS and APLA were rare causes of thrombocytopenia in our hospital. Of the 96 cases enrolled in the study, 88 were diagnosed during pregnancy. Amongst the hypertensive disorders, 16.7% was due to gestational hypertension, 10.4% due to preeclampsia and 7.4% were due to HELLP syndrome. 82.3% of patients with thrombocytopenia in this study were asymptomatic.

Conclusions: Thrombocytopenia should be evaluated by making a practice of routinely checking the platelet count and peripheral smear in early pregnancy and also in third trimester to enable early diagnosis since most cases may be asymptomatic.

Keywords: Gestational thrombocytopenia, ITP, Preeclampsia

INTRODUCTION

Thrombocytopenia in pregnancy, may result from several etiologies which include those that are unique to pregnancy and others which may occur in non pregnant settings.¹ They include gestational thrombocytopenia, hypertensive disorders of pregnancy like preeclampsia, eclampsia and HELLP syndrome, liver diseases including acute fatty liver of pregnancy, drug induced thrombocytopenia, immune thrombocytopenia, thrombocytopenia due to viral infections, SLE, APLA syndromes. Awareness of these causes, facilitates proper diagnosis and management of thrombocytopenia in the

pregnant women. Normal pregnancy is associated with a physiologic fall in the platelet count. The reason for this decline is not known, although it has been speculated that these changes may reflect dilution, decreased platelet production, or increased platelet turnover during pregnancy.² The fall in the platelet in some pregnant women results in platelet counts that fall into the thrombocytopenic range.³

Thrombocytopenia is classically defined as a platelet count of less than $150 \times 10^9 / L$.⁴ Counts to 100 to $150 \times 10^9 / L$ are considered mildly depressed, 50 to $100 \times 10^9 / L$ are moderately depressed and less than $50 \times 10^9 / L$ are

severely depressed.⁵ Thrombocytopenia is second only to anemia as the most common hematologic abnormality during pregnancy.⁶ The overall incidence of thrombocytopenia in pregnancy is 8%, but when patients with obstetric or medical conditions are excluded, the incidence drops to 5.1%.⁶ The most common cause is gestational thrombocytopenia which accounts for around 70% cases. Hypertensive disorders account for 21% which includes preeclampsia, eclampsia, and HELLP syndrome. Immune-mediated thrombocytopenia, including idiopathic thrombocytopenic purpura is responsible for 4.1% of cases, which is a proportionally small number. These conditions, however, can cause considerable morbidity and mortality, and they must be managed closely. Thrombocytopenia can have a wide range of prognostic implications, from completely benign to life threatening.⁷

Gestational thrombocytopenia, which is seen in about 5% pregnancies, is a benign phenomenon. In this condition however platelet counts usually remain above $100 \times 10^9/L$, but can fall to $70 \times 10^9/L$. This condition usually occurs in the late second or third trimesters of pregnancy. The aetiology may be due to increased peripheral consumption of platelets. An immune mechanism is also postulated. It is usually a diagnosis of exclusion. It usually requires routine prenatal care and monitoring of platelet count every 4 weeks. Mode of delivery is as per maternal and fetal indications. Epidural anaesthesia is safe at counts above one lakh. Recurrence of gestational thrombocytopenia in subsequent pregnancies is common and patient should be properly counselled about this. It has features overlapping ITP. History of thrombocytopenia before 28 weeks and a platelet count less than $50 \times 10^9/L$ is highly suggestive of ITP. Gestational thrombocytopenia resolves spontaneously after delivery within 6 weeks postpartum. In ITP most often there is a history of bleeding outside pregnancy and low platelet counts prior to pregnancy. Management in ITP is directed towards raising platelet counts to prevent spontaneous bleeding and ensure safe delivery. Treatment of ITP in pregnancy is mainly steroids and IVIG though the response is lesser in pregnant than non-pregnant patients. Generally treatment is required only in the third trimester and aim is to keep the values above $50 \times 10^9/L$. Due to the increased risk of neonatal thrombocytopenia instrumental delivery should be avoided in cases of maternal ITP.

Immune thrombocytopenia due to production of IgG antiplatelet antibodies against own platelet membrane glycoprotein's is characterized by, moderate thrombocytopenia, is an early gestation platelet count below one lakh, and increased megakaryocyte level on bone marrow biopsy. Pregnancy does not worsen the course of this condition but cases of severe thrombocytopenia can cause severe morbidity and mortality to the fetus.⁸ This condition usually requires treatment with IVIG and steroids. Platelet transfusions

may be less effective in view of ongoing platelet destruction.

Preeclampsia is a common cause of thrombocytopenia in third trimester of pregnancy. The risk of development of thrombocytopenia is about 18% in preeclampsia, 10-12% in DIC and 4-15% in HELLP syndrome.⁹ The general approach in these cases would be medical stabilization and expeditious delivery after 34 weeks. If earlier then maternal well being has the priority.

Thrombocytopenia may be related to liver disease and hypersplenism in pregnancy. Most liver disease in pregnancy is attributable to 1 of the 5 liver diseases unique to pregnancy: hyperemesis gravidarum, intrahepatic cholestasis of pregnancy, preeclampsia, HELLP syndrome, and acute fatty liver of pregnancy. Of these disorders, only HELLP, preeclampsia, and acute fatty liver of pregnancy are associated with thrombocytopenia. A recent study showed that 47% of patients had platelet count less than $100 \times 10^9/L$. Management of AFLP is immediate termination of pregnancy. Coagulation studies should be optimized by transfusion prior to delivery.

Systemic lupus erythematosus (SLE) predominantly affects women of childbearing age. Disease flares during SLE pregnancy pose challenges with respect to distinguishing physiologic changes related to pregnancy from disease related manifestations. So a multidisciplinary approach with close medical, obstetric, and neonatal monitoring is necessary to optimize both maternal and fetal outcomes.¹⁰ Thrombocytopenia less than $100 \times 10^9/L$ is one of the diagnostic criteria of SLE. The thrombocytopenia of SLE rarely becomes severe. If treatment is required in severe thrombocytopenia, patients may respond to hydroxychloroquine, glucocorticoids, or other immunosuppressive medications used for other manifestations of SLE.¹¹ Heparin induced thrombocytopenia (HIT) occurs in 1% to 5% of patients receiving unfractionated heparin within the previous 5 to 10 days. HIT is an extremely thrombotic process, despite the low platelet count.

Analgesics like aspirin, acetaminophen, antibiotics like penicillin and drugs like heparin, methyl dopa, digitalis, and cyclosporine may cause thrombocytopenia. It is recommended to obtain a baseline platelet count before starting therapy, then repeat platelet counts on Days 7 and 14 of therapy. HIT should be suspected if the platelet count falls by approximately 50% or more. If the repeat platelet counts are normal, no further testing is necessary.

Chronic infection with HIV and HCV are frequent causes of chronic thrombocytopenia. Treatment of HIV and HCV related thrombocytopenia should be directed toward antiviral therapy with highly active antiretroviral therapy regimens. The antiphospholipid antibody syndrome is an autoimmune disorder which associates clinical thromboembolism with obstetric manifestations.

Antiphospholipid antibodies cause obstetric accidents by a thrombocytopenia phenomenon.¹²

METHODS

This was a case control study conducted in a tertiary referral Medical College Hospital in, Trivandrum, Kerala, India in the Department of Obstetrics and Gynecology.

Study population: Antenatal women attending SAT hospital, Trivandrum.

Sample size: Sample size was calculated using the prevalence noted in study conducted in Israel, where prevalence of HELLP syndrome amongst cases was 18% and in control group was 4.7%.¹³ Incidence of HELLP in OBG department in SAT hospital is 1%. The Odds ratio calculated was 4.45%. Using these assumptions sample size was calculated as 90 patients as cases and 90 patients as controls. Sample size was calculated using the formula:

$$n = \frac{\left\{ Z_{1-\frac{\alpha}{2}} \sqrt{2\bar{P}^*(1-\bar{P}^*)} + Z_{1-\beta} \sqrt{P_1^*(1-P_1^*) + P_2^*(1-P_2^*)} \right\}^2}{(P_1^* - P_2^*)^2}$$

Where,

$$P_1^* = \frac{(OR)P_2^*}{(OR)P_2^* + (1 - P_2^*)}$$

$$\bar{P}^* = \frac{P_1^* + P_2^*}{2}$$

P₁*: Probability of exposure given disease present

P₂*: Probability of exposure given disease absent

OR: Anticipated odds ratio

α: Significance level

1-β: Power

Where P₁ is 18, P₂ is 4.75, Power is 80%, Odd's ratio is 4.45%, and Alpha error is 5%

Sampling technique: Purposive sampling

Inclusion criteria: Antenatal women attending SAT hospital at any gestational age with platelet count below 150 ×10⁹/L including referred patients.

Exclusion criteria: Those who are not willing to participate in the study and patients with normal platelet count.

Study duration: 18 months

Definition of terms: Cases were defined as antenatal women of any gestational age with platelet count less than 150 ×10⁹/L, mild cases defined as when platelet count is between 100 and 150 ×10⁹/L, moderate when platelet count is between 50 and 100 ×10⁹/L, severe when count is below 50×10⁹/L⁶⁹.

Controls were defined as consecutive antenatal women of any gestational age with normal platelet count

Data collection tools: Structured questionnaire

Data collection process: After informed consent, pregnant women were interviewed for detailed socioeconomic, demographic, past, personal and family history. Complete blood count was done by using automated cell counters in haematology lab of SAT hospital; same was confirmed by doing peripheral blood smear examination. For referred patients to SAT hospital thrombocytopenia was confirmed in haematology lab by doing complete blood count and peripheral blood smear examination.

Data analysis: Qualitative variables were expressed in frequency distribution. Data analysis was performed using SPSS version 22. Between groups comparison of qualitative variables were analyzed by chi-square test. A p value of 0.05 was taken as the level of significance.

RESULTS

Sociodemographic characteristics: There were 96 patients in the cases group and 96 in the control group. In this study age of the patient, socioeconomic class and gestational age at presentation did not prove to be statistically significant. So they were not found to be a risk factor of thrombocytopenia.

Table 1: Distribution of hypertensive disorders amongst cases and controls.

Hypertensive disorders	Category				Total	
	Case		Control			
	N	%	N	%	N	%
Yes	35	36.5	10	10.4	45	23.4
No	61	63.5	86	89.6	147	76.6
Total	96	100	96	100	192	100
χ ² = 18.141	p<0.001		OR=4.934-2.272		95% CI for OR=10.717	

Parity: 55 patients were of primiparity and 41 were multiparous amongst “cases” and 60 patients were primi and 36 were multiparous amongst the “controls”. This was not statistically significant and parity was not a risk factor for thrombocytopenia.

Past obstetric history: 22 cases and 21 controls had previous abortions. History of IUD was noted in 5 patients in the control group and none in the case group. There was no history of still birth among patients with thrombocytopenia but 5 patients in the control group had history of still birth. Past obstetric history was not found to be a risk factor for thrombocytopenia.

Table 2: Hypertensive disorders sub classified amongst cases and controls.

Maternal diseases	Category				Total	
	Case		Control			
	N	%	N	%	N	%
None	61	63.5	86	89.6	147	76.6
Gestational HTN	16	16.7	6	6.3	22	11.5
Preeclampsia	10	10.4	1	1	11	5.7
C/C Hypertension	2	2.1	3	3.1	5	2.6
HELLP	7	7.3	0	0	7	3.6
Total	96	100	96	100	192	100

Table 3: Distribution of ITP between cases and controls.

Known case of ITP	Category				Total	
	Case		Control			
	N	%	N	%	N	%
Yes	10	10.4	2	2.1	12	6.3
No	86	89.6	94	97.9	180	93.8
Total	96	100	96	100	192	100
$\chi^2=5.689$	p=0.017		OR=5.465		95% CI for OR=1.164-25.648	

Table 4: Platelet count at admission in cases.

Platelet count at admission	Case	
	N	%
<50000	11	11.5
51000-99999	39	40.6
100000-150000	46	47.9
Total	96	100

Presence of hypertensive disorders: Among 96 cases of thrombocytopenia, around 36.5% (n=35) of patient had hypertensive disorder of pregnancy. Among the control group 10.4% of (n=10) had hypertensive disorder of pregnancy. Hence hypertensive disorder of pregnancy was as a risk factor for thrombocytopenia ($p < 0.001$) in this study (Table 1). Of the 35 cases with hypertensive disorders, 16 cases (16.7%) were due to gestational hypertension, 10 cases (10.4%) were due to preeclampsia, 7 cases (7.3%) were due to HELLP, and 2 case (2.2%) were due to chronic hypertension (Table 2). Presence of ITP: There were 10 patients with ITP in the cases group and only 2 patients in the control group. History of ITP

was a significant risk factor of thrombocytopenia in pregnancy ($p < 0.017$) (Table 3).

History of thyroid disorders: 11.5% of cases and 17.7% of control group had history of hypothyroidism which was not a statistically significant risk factor. There were only 2 women with hyperthyroidism among cases.

History of GDM: There were 7 women among cases 2 among the control group who had GDM. Rest was not having this history. Presence of gestational diabetes was not a significant risk factor for thrombocytopenia.

History of hypertension: Past history of hypertension was not a significant risk factor.

Presence of gestational thrombocytopenia: 47 out of 96 women had gestational thrombocytopenia. So this was the commonest cause of thrombocytopenia in this study.

Platelet count at admission: 47.9% of patients had mild thrombocytopenia, 40.6% had moderate thrombocytopenia and 11.5% had severe

thrombocytopenia. Using peripheral smear examination 51% had mild thrombocytopenia, 33.3% of patients had moderate thrombocytopenia, 9.4% had severe thrombocytopenia and 6.3% had thrombocytopenia with haemolysis. (Table 4 and 5)

Treatment modalities: 26 out of 96 cases with thrombocytopenia required some form of treatment. 8 patients needed platelet transfusion, 6 patients needed

oral prednisolone, one needed I/V methyl prednisolone, 3 patients needed both steroid and platelet transfusion. There was one patient who needed parenteral as well as oral prednisolone along with platelet transfusion.

History of heparin intake: 9 patients out of 96 had a history of heparin intake. Among the control group 4 patients had a history of heparin intake. This was not found to be statistically significant risk factor.

Table 5: Platelet counts sub classified according to severity in peripheral smear.

Peripheral smear	Category				Total	
	Case		Control			
	N	%	N	%	N	%
Mild thrombocytopenia	49	51	0	0	49	25.5
Moderate thrombocytopenia	32	33.3	0	0	32	16.7
Severe thrombocytopenia	9	9.4	0	0	9	4.7
Thrombocytopenia and haemolysis	6	6.3	0	0	6	3.1
Not applicable	0	0	93	96.9	93	48.4
Total	96	100	96	100	192	100

History of intake of antibiotics: There is no significant difference between cases and control group when we compare h/o antibiotic intake causing thrombocytopenia ($p=0.112$).

Other medical disorders: In this study there were 7 cases of APLA, 5 cases of SLE, 2 cases of dengue infection and one case each of Rheumatoid arthritis, AFLP and HUS was there which was not a statistically significant risk factor in this study probably due to small numbers.

DISCUSSION

This study sought to determine the risk factors of thrombocytopenia among the antenatal patients attending our hospital.

Although most cases of thrombocytopenia in pregnancy do not result in adverse outcomes, the underlying pathology can sometimes be life threatening so once thrombocytopenia is diagnosed in pregnancy woman should undergo further clinical and laboratory evaluation to determine the cause. Careful analysis of time of onset of thrombocytopenia and clinical manifestations is critical to provide timely diagnosis and appropriate maternal and fetal care.

In our study, gestational thrombocytopenia was the most common cause of thrombocytopenia (49%). Around 17% of cases were due to Preeclampsia-HELLP syndrome and 10.4% of patients had ITP. In a study by Vyas et al in Ahmadabad, of the 4818 patients studied, gestational thrombocytopenia was the commonest aetiology

(44.6%).¹⁴ Incidence of thrombocytopenia due to severe preeclampsia and HELLP syndrome was 22%. Incidence of ITP was 4.4%. These results were consistent with the results of our study. However, in the above mentioned study pregnant women with mild thrombocytopenia were taken as the control group whereas in our study normal pregnant women were taken as the control group. In another study conducted by Parnat et al in Soroka University Medical Centre, Israel the main causes of thrombocytopenia were gestational thrombocytopenia (GT) (59.3%), immune thrombocytopenic purpura (ITP) (11.05%), preeclampsia (10.05%), and HELLP syndrome (12.06%).¹³ There was only one case of APLA. Their study results were consistent with our study findings. However in their study patients with mild thrombocytopenia were not included in the study group.

95% of cases in our study presented in the third trimester and gestational thrombocytopenia (46.5%) was the most common cause in this trimester. There was only 1 case of AFLP. In a study done by Mamatha S et al in M. S. Ramaiah Medical College, Bangalore, 46.6% of cases were due to gestational thrombocytopenia and 46.6% of cases were due to HELLP and preeclampsia and 2 cases were due to AFLP. About 60% of the patients presented in third trimester, closely followed by 40% in second trimester. In this difference could be due to the very small sample size ($n=30$) in the study done by Mamatha S et al compared to the sample size in our study ($n=96$).

In another study done by Salnlo et al, in Helsinki University Central Hospital, Finland, most cases (81%) of maternal thrombocytopenia at term were due to gestational thrombocytopenia.¹⁶ Other causes of

thrombocytopenia were preeclampsia (16%) and idiopathic thrombocytopenic purpura (ITP) (3%). This study results were consistent with our study findings which shows that gestational thrombocytopenia is the most common cause of thrombocytopenia in pregnancy followed by hypertensive disorder of pregnancy (36.5%).

In this study 51% of patients had mild thrombocytopenia, 33.3% of patient had moderate thrombocytopenia and 9.4% of patient had severe thrombocytopenia. In a study by Katke RD et al, 70.9% patients had moderate, 29.1% patients had severe thrombocytopenia.¹⁷ This difference might be due to the large number of patients included in their study and also could be due to the non-inclusion of patients with mild thrombocytopenia in their study. In their study, 35% cases were primipara, 32% cases were gravida 2, 33% cases were gravida 3 to 5. In our study 57% of cases were primipara and 43% were multipara. As the difference is not significant, parity was not proven as a risk factor for thrombocytopenia according to our study. Gestational thrombocytopenia was the most common etiological factor with 30.1% cases. 27.2% cases were due to hypertensive disorders, 18.4% cases due to malaria followed by 12.6% cases due to dengue in their study. There were 2 cases of dengue fever with thrombocytopenia in our study and no case of malaria was found in our study. This could be because both Dengue and Malaria are less common in Kerala compared to North India.

Another study done by Nisha S et al in CSMMU, Lucknow, gestational thrombocytopenia was seen in 64.2%, followed by thrombocytopenia due to hypertensive disorders of pregnancy. The results of this study were consistent with our study findings.¹⁸

In a study done in Ege University in Turkey assessing thrombocytopenia in pregnancy, around 43.5% of thrombocytopenia was due to HELLP syndrome followed by gestational thrombocytopenia (39.5%) and ITP was around 16%.¹⁹ Fifty percent of patients were primigravida and 14% of patients had advanced maternal age. In our study as well as several other studies gestational thrombocytopenia was the most common cause of thrombocytopenia.

All cases of thrombocytopenia require an early detection and appropriate treatment according to the diagnosis. Babies also need to be evaluated for neonatal thrombocytopenia. The risk of neonatal thrombocytopenia in babies born to mothers with gestational thrombocytopenia is considered negligible.

CONCLUSION

Gestational thrombocytopenia is the most common cause of thrombocytopenia (49%). Most of the gestational thrombocytopenia is incidental findings. 82.3% of patients with thrombocytopenia were asymptomatic. Hypertensive disorder of pregnancy were the second

most cause of thrombocytopenia in pregnancy (39.5%), of which 16.7% were due to GHTN, 10.4% were due to preeclampsia and 7.4% were due to HELLP syndrome. 10.4% of cases were due to ITP. 51% of patients had mild thrombocytopenia, 33.3% had moderate thrombocytopenia and 9.4% had severe thrombocytopenia. SLE, AFLP, Dengue infection, HUS and APLA are the rare causes of thrombocytopenia in SAT hospital.

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