Moderate to Severe Thrombocytopenia During Pregnancy: A Single Institutional Experience

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Abstract Most of thrombocytopenic pregnant women present mild decrease of platelet counts and have favorable outcome. However, small portion of these cases can show moderate to severe thrombocytopenia and may increase the risk of bleeding during delivery. We investigated the prevalence, causes, and outcomes of pregnancies complicated by moderate to severe thrombocytopenia. We reviewed medical records of pregnant women who were diagnosed with moderate to severe thrombocytopenia ($<100 \times 10^9/L$) during their pregnancies. A total of 4822 deliveries were performed and 26 patients (0.54%) with moderate to severe thrombocytopenia were identified. The most common cause of moderate to severe thrombocytopenia was immune thrombocytopenia (ITP) (42.3%), followed by gestational thrombocytopenia (GT) (34.6%). Compared to GT, ITP showed lower platelet counts at presentation ($52.4 \times 10^9/L$ vs. $80.5 \times 10^9/L$, $P = 0.041$). Patients with GT could conduct successful delivery without specific management, and patients with ITP showed favorable delivery outcomes with adequate treatment. In conclusion, the incidence of moderate to severe thrombocytopenia during pregnancy was very low and most

common causes were ITP and GT. Patients with moderate to severe thrombocytopenia could have favorable delivery outcomes with adequate treatment.

Keywords Thrombocytopenia · Pregnancy · Gestational thrombocytopenia · Immune thrombocytopenia

Introduction

The overall incidence of thrombocytopenia in pregnancy is between 6.6 and 11.6% [1, 2]. There are many potential causes of pregnancy-associated thrombocytopenia. Some of them, such as gestational thrombocytopenia (GT), preeclampsia, and HELLP (hemolysis, elevated liver function tests, low platelets) syndrome, are unique to pregnancy, while others including immune thrombocytopenia (ITP), systemic lupus erythematosus (SLE), antiphospholipid antibodies syndrome (APLA), or bone marrow dysfunction may also occur in the non-pregnant conditions. Among these diverse causes, GT which is known to have benign clinical course is most commonly diagnosed, accounting for 70–80% of cases followed by hypertensive disorder (15–20%) and ITP (3–4%) [3].

Thrombocytopenia is classified as mild with a platelet count of $100\text{--}150 \times 10^9/L$, moderate with $50\text{--}100 \times 10^9/L$, and severe with less than $50 \times 10^9/L$. Most of platelet disorders occurred during pregnancy is mild thrombocytopenia, and moderate to severe thrombocytopenia are observed in only 1% of pregnant women [4].

The prognosis of mild thrombocytopenia which is usually caused by GT is favorable without serious delivery-related complications [5]. However, moderate to severe thrombocytopenia caused by other conditions rather than GT may compromise epidural anesthesia or increase the

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risk of bleeding during delivery. Since therapeutic interventions may have unique toxicities to both mother and fetus, differential diagnosis and management for moderate to severe thrombocytopenia should be carefully approached.

Considering this clinical importance, we focused on patients who developed moderate to severe thrombocytopenia during their pregnancy. The aim of this study was to investigate the prevalence, causes, and outcomes of pregnancies complicated by moderate to severe thrombocytopenia.

Patients and Methods

Patients

This retrospective study was approved with a waiver of patients' informed consent by the Institutional Review Board. We reviewed the medical records of pregnant women whose thrombocytopenia was first detected during their pregnancies at Kangnam Sacred-Heart Hospital, Seoul, South Korea, between August 2010 and December 2015. The pregnant women with moderate to severe thrombocytopenia (platelet count below $100 \times 10^9/L$) were included in the study. The following data was extracted from the medical records for each eligible patient: maternal age, previous gestations, parity, underlying medical conditions, medication, serial platelet counts (during pregnancy, at delivery and in the postpartum period), signs and symptoms of hemostatic impairment, treatments provided to raise platelet counts, gestational age at delivery, type of delivery [vaginal or cesarean section (CS)], epidural anesthesia during delivery, blood products transfused, and complications at delivery and in the postpartum period.

Diagnosis of ITP, GT, and Preeclampsia

The diagnosis of ITP or GT in the thrombocytopenic women was made on clinical grounds, based upon the diagnostic criteria previously suggested in the relevant literature [6]. Patients were considered to have GT if the platelet counts returned to normal within 12 weeks of delivery, whereas diagnosis of ITP was made whenever this was not the case. No patients received bone marrow examinations for the differential diagnosis of thrombocytopenia. Criteria for the diagnosis of preeclampsia, which had been defined by the American College of Obstetricians and Gynecologists, included the followings [7]: (1) blood pressure of 140 mm Hg systolic or 90 mm Hg diastolic or higher that occurs after 20 weeks of gestation in a woman with previously normal blood pressure; and (2) proteinuria,

defined as urinary excretion of 0.3 g of protein or higher in a 24-hour specimen, that usually correlates with a 1+ or greater reading on dipstick.

Statistical Analysis

Demographic and clinical data were described with mean $\pm$ standard deviation (SD), frequency, and percentage. The variables between two groups were compared using the Mann–Whitney U-test or Fisher's exact test. A *P* value of 0.05 or less was considered statistically significant.

Results

Patients' Characteristics

A total of 4822 deliveries were performed, and 101 patients (2.1%) showed thrombocytopenia (platelet count below $150 \times 10^9/L$) during their pregnancy. In all patients, thrombocytopenia was detected by routine blood examination with no sign of abnormal bleeding. Among these thrombocytopenic patients, 26 patients (26/4822, 0.54%) with moderate to severe thrombocytopenia were identified. Clinical characteristics of these patients are summarized in Table 1. Mean age of the patients was 29.7 ± 5.0 years, and 17 of 26 patients (65.4%) were nullipara. At the time of diagnosis of moderate to severe thrombocytopenia, 15.4% (4/26) of cases were of <37 weeks of gestation, 65.4% (17/26) were between 37 and 39 weeks of gestation, and 19.2% (5/26) had gestational age of >40 weeks.

Table 1 Clinical characteristics of pregnant women with moderate to severe thrombocytopenia

Variables	n = 26 (%)
Maternal age (mean years $\pm$ S.D.)	29.7 $\pm$ 5.0
Previous gestations	
0	12 (46.2%)
1	5 (19.2%)
2	3 (11.5%)
3	3 (11.5%)
4	3 (11.5%)
Parity	
0	17 (65.4%)
1	6 (23.1%)
2	3 (11.5%)
Gestational age	
<37 weeks	4 (15.4%)
37–39 weeks	17 (65.4%)
>40 weeks	5 (19.2%)

The most common cause of moderate to severe thrombocytopenia was ITP (11/26, 42.3%), followed by GT (9/26, 34.6%). Other etiologies included preeclampsia (2), vitamin B12 deficiency (2), liver cirrhosis (1), and thrombotic thrombocytopenic purpura (1) (Table 2).

Comparison of ITP and GT Patients

Table 3 shows the comparison of clinical variables between patients with ITP and GT. Mean gestational age at the time of diagnosis was within third trimester in both ITP and GT. Compared to patients with GT, patients with ITP had lower platelet counts at presentation ($52.4 \pm 32.6 \times 10^9/L$ vs. $80.5 \pm 19.0 \times 10^9/L$, $P = 0.041$). In this study with a small number of patients, however, there were no significant statistical differences of other variables between patients with ITP and those with GT.

Treatment

We had no specific treatment guidelines for thrombocytopenia during pregnancy. In clinical practice, however, we performed vaginal delivery without transfusion or disease-specific treatment if patient's platelet count was more than $75 \times 10^9/L$. When patient's platelet count was less than $50 \times 10^9/L$, we considered platelet transfusion right before delivery regardless of underlying disease. If platelet counts of patients with ITP were less than $50 \times 10^9/L$, we considered steroid with or without immunoglobulin.

Eight patients with GT performed vaginal delivery successfully without specific treatment for thrombocytopenia. Six out of 11 ITP patients with platelet count less than $75 \times 10^9/L$ received platelet transfusion without disease-specific treatment right before vaginal delivery. Three ITP patients with platelet count less than $50 \times 10^9/L$ received specific treatment for ITP. Two patients were treated with steroid as first-line treatment and achieved response. The remaining one patient showed no response to initial steroid. She received steroid plus intravenous immunoglobulin as

second-line treatment but failed to achieve response and received platelet transfusion before delivery. Patients with other causes including preeclampsia, vitamin B12 deficiency, liver cirrhosis, and TTP didn't receive platelet transfusion before delivery because their platelet counts were more than $75 \times 10^9/L$ at the time of delivery.

Delivery Outcomes

In most patients except for 4, full-term delivery was possible. Two patients with preeclampsia and 2 with ITP had preterm delivery. Nineteen patients underwent vaginal delivery. The remaining 7 patients (4 with ITP and 3 with GT) received CS, but thrombocytopenia was not the reason for CS in these patients. There were no patients showing significant bleeding during peripartum period.

Discussion

Mild thrombocytopenia ($>100 \times 10^9/L$) during pregnancy usually has no clinical significance [2]. However, patients with moderate to severe thrombocytopenia can develop bleeding complication during peripartum period. In the current study, we retrospectively reviewed the etiology and clinical outcomes of pregnant women with moderate to severe thrombocytopenia. ITP (42.3%) and GT (30.8%) were most common causes of these cases. All patients with GT had a benign clinical course without any delivery-related complications, and patients with ITP also showed favorable outcomes with adequate management.

ITP accounts for small portion (3% of cases) of thrombocytopenic pregnant women, compared to GT (70–80% of cases) [3]. In cases of moderate to severe thrombocytopenia, however, the incidence of ITP was higher because more than two-thirds of women with GT have platelet counts of $130\text{--}150 \times 10^9/L$ and only less than 10% of GT cases present with moderate to severe thrombocytopenia [8].

Distinguishing ITP from GT may be problematic because both disorders are diagnosis of exclusion. Based on the data that ITP has relatively lower platelet count at diagnosis and occurs earlier in the gestational stage, McCrae et al. [9] suggested that developing a platelet count $<100 \times 10^9/L$ early in pregnancy, with declining platelet counts as gestation progresses, is consistent with ITP. GT is frequently developed in third trimester and the platelet count normalizes within 2 weeks after delivery. Because there were very few cases of GT with counts $40\text{--}50 \times 10^9/L$ [5, 8], we ruled out a diagnosis of gestational thrombocytopenia if the platelet count was $<50 \times 10^9/L$. In this study with a small number of subjects, patients with ITP

Table 2 Etiology of moderate to severe thrombocytopenia in the study group

Causes	n = 26 (%)
Immune thrombocytopenia	11 (42.3%)
Gestational thrombocytopenia	9 (34.6%)
Preeclampsia	2 (7.7%)
Vitamin B12 deficiency	2 (7.7%)
Liver cirrhosis	1 (3.8%)
Thrombotic thrombocytopenic purpura	1 (3.8%)

Table 3 Comparison of immune thrombocytopenia and gestational thrombocytopenia

Clinical variables	ITP (mean $\pm$ SD) (n = 11)	GT (mean $\pm$ SD) (n = 9)	P value
Maternal age (years)	28.5 $\pm$ 5.7	28.6 $\pm$ 4.7	0.973
Nullipara	6 (54.5%)	5 (55.6%)	1.000
GA at diagnosis (weeks)	31.5 $\pm$ 10.9	35.5 $\pm$ 6.9	0.344
Platelet count at diagnosis ($\times 10^9/L$)	52.4 $\pm$ 32.6	80.5 $\pm$ 19.0	0.041
GA at nadir of platelet count (weeks)	31.6 $\pm$ 10.9	38.2 $\pm$ 1.5	0.107
Platelet count at nadir ($\times 10^9/L$)	51.8 $\pm$ 33.6	74.8 $\pm$ 22.7	0.102
Delivery weeks	38.4 $\pm$ 2.5	38.8 $\pm$ 0.6	0.667
Platelet count at delivery day ($\times 10^9/L$)	81.4 $\pm$ 37.5	97.6 $\pm$ 21.5	0.600
Delivery mode (vaginal/cesarean)	7/4	6/3	1.000
Platelet count after delivery within 1 week ($\times 10^9/L$)	96.8 $\pm$ 28.5	127.0 $\pm$ 46.8	0.107

ITP Immune thrombocytopenia, GA Gestational age, GT Gestational thrombocytopenia

showed lower platelet count at presentation than those with GT ($52.4 \times 10^9/L$ vs. $80.5 \times 10^9/L$, $P = 0.041$).

Pregnant women with GT, even though they have moderate thrombocytopenia (50 – $100 \times 10^9/L$), are known to have favorable delivery outcomes without specific treatment [1]. In our study, all patients with GT conducted successful delivery without bleeding complication. Pregnant patients with ITP are at risk for spontaneous bleeding and complications during peripartum period, particularly if the platelet counts drop to less than $20 \times 10^9/L$. First-line treatment is similar to that of nonpregnant women with newly diagnosed ITP and systemic corticosteroid is recommended [10, 11]. Two thirds of patients respond to initial steroid treatment [12], but steroid can exacerbate hypertension and induce hyperglycemia. Corticosteroid may contribute to adverse pregnancy outcome in some patients [13]. If steroid is not successful or when side effects of steroid are poorly tolerated, intravenous immunoglobulin and splenectomy can be used as a second-line treatment, either alone or in combination with steroid [14, 15]. Anti Rh-D immunoglobulin, cyclophosphamide and vinca alkaloids are not considered safe during pregnancy, and limited data are available for other agents including rituximab, danazol [16, 17]. Thrombopoietin receptor agonist which is recently adopted as one of the second-line treatment for ITP is not well studied in the pregnant woman. Interestingly, two cases of pregnant women with refractory ITP who were successfully treated with romiplostim were recently reported [18]. In this study, 3 ITP patients with platelet count less than $<50 \times 10^9/L$ received specific treatment for thrombocytopenia. Two patients who received steroid treatment achieved response and their platelet count reached over $50 \times 10^9/L$ at the time of delivery. One patient who didn't response to steroid treatment received additional intravenous immunoglobulin with steroid but failed to achieve response. She received

platelet transfusion before delivery and underwent vaginal delivery without complications.

ITP alone is not an indication for cesarean delivery [10, 11]. Uncomplicated vaginal delivery has been reported even in several ITP cases with platelet counts 20 – $50 \times 10^9/L$ [19, 20]. However, patients with platelet count less than $50 \times 10^9/L$ are at risk of life threatening bleeding during vaginal delivery. Various treatment combinations of platelets transfusion, steroid, IVIG, or splenectomy can be used to reach the optimal platelet count. Prophylactic platelet transfusions are not usually recommended in ITP patients [9]. In clinical practice, however, physicians often perform platelet transfusion for patients with ITP right before delivery. In our hospital, if patient's platelet count was less than $50 \times 10^9/L$, we considered platelet transfusion as an institutional practice. In this study, all patients with ITP reached platelet count over $50 \times 10^9/L$ with adequate treatment and platelet transfusion before delivery. Among 11 ITP patients, 7 patients underwent vaginal delivery and 4 patients received CS without major bleeding complication.

This study has an inherent selection bias caused by its retrospective nature. Despite of this major limitation, this study has advantages with a relatively large number of pregnant women included in the analysis and the scope focused on moderate to severe thrombocytopenia which has clinical significance.

In conclusion, the incidence of moderate to severe thrombocytopenia during pregnancy was very low, and most common causes were ITP and GT. Patients with moderate to severe thrombocytopenia diagnosed during pregnancy could have favorable delivery outcomes with adequate treatment.

Compliance with Ethical Standards

Conflict of interest The authors have no conflict of interest.

References

- Burrows RF, Kelton JG (1993) Fetal thrombocytopenia and its relation to maternal thrombocytopenia. *N Engl J Med* 329:1463–1466
- Boehlen F, Hohlfeld P, Extermann P, Perneger TV, de Moerloose P (2000) Platelet count at term pregnancy: a reappraisal of the threshold. *Obstet Gynecol* 95:29–33
- Verdy E, Bessous V, Dreyfus M, Kaplan C, Tchernia G, Uzan S (1997) Longitudinal analysis of platelet count and volume in normal pregnancy. *Thromb Haemost* 77:806–807
- Sainio S, Kekomäki R, Riikonen S, Teramo K (2000) Maternal thrombocytopenia at term: a population-based study. *Acta Obstet Gynecol Scand* 79:744–749
- Burrows RF, Kelton JG (1990) Thrombocytopenia at delivery: a prospective survey of 6715 deliveries. *Am J Obstet Gynecol* 162:731–734
- Gernsheimer T, McCrae KR (2007) Immune thrombocytopenic purpura in pregnancy. *Curr Opin Hematol* 14:574–580
- American College of Obstetricians and Gynecologists (2013) Task force on hypertension in pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' task force on hypertension in pregnancy. *Obstet Gynecol* 122:1122–1131
- Win N, Rowley M, Pollard C, Beard J, Hambley H, Booker M (2005) Severe gestational (incidental) thrombocytopenia: to treat or not to treat. *Hematology* 10:69–72
- McCrae KR (2003) Thrombocytopenia in pregnancy: differential diagnosis, pathogenesis, and management. *Blood Rev* 17:7–14
- Provan D, Stasi R, Newland AC, Blanchette VS, Bolton-Maggs P, Bussell JB, Chong BH, Cines DB, Gernsheimer TB, Godeau B, Grainger J, Greer I, Hunt BJ, Imbach PA, Lyons G, McMillan R, Rodeghiero F, Sanz MA, Tarantino M, Watson S, Young J, Kuter DJ (2010) International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood* 115:168–186
- Neunert C, Lim W, Crowther M, Cohen A, Solberg L, Crowther MA (2011) The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood* 117:4190–4207
- Sullivan CA, Martin JN Jr (1995) Management of the obstetric patient with thrombocytopenia. *Clin Obstet Gynecol* 38:521–534
- Laskin CA, Bombardier C, Hannah ME, Mandel FP, Ritchie JW, Farewell V, Farine D, Spitzer K, Fielding L, Soloninka CA, Yeung M (1997) Prednisone and aspirin in women with autoantibodies and unexplained recurrent fetal loss. *N Engl J Med* 337:148–153
- Anglin BV, Rutherford C, Ramus R, Lieser M, Jones DB (2001) Immune thrombocytopenic purpura during pregnancy: laparoscopic treatment. *JSLs* 5:63–67
- Griffiths J, Sia W, Shapiro AMJ, Tataryn I, Turner AR (2005) Laparoscopic splenectomy for the treatment of refractory immune thrombocytopenia in pregnancy. *J Obstet Gynaecol Can* 27:771–774
- Chakravarty EF, Murray ER, Kelman A, Farmer P (2011) Pregnancy outcomes after maternal exposure to rituximab. *Blood* 117:1499–1506
- Orisaka M, Shukunami K-I, Orisaka S, Goto K, Yoshida Y, Kotsuji F (2005) Combination therapy for a pregnant woman with severe refractory ITP. *Eur J Obstet Gynecol Reprod Biol* 121:119–120
- Decroocq J, Marcellin L, Le Ray C, Willems L (2014) Rescue therapy with romiplostim for refractory primary immune thrombocytopenia during pregnancy. *Obstet Gynecol* 124:481–483
- Webert KE, Mittal R, Sigouin C, Heddle NM, Kelton JG (2003) A retrospective 11-year analysis of obstetric patients with idiopathic thrombocytopenic purpura. *Blood* 102:4306–4311
- Koyama S, Tomimatsu T, Kanagawa T, Kumasawa K, Tsutsui T, Kimura T (2012) Reliable predictors of neonatal immune thrombocytopenia in pregnant women with idiopathic thrombocytopenic purpura. *Am J Hematol* 87:15–21