Etiology And Outcomes Of Moderate To Severe Thrombocytopenia During Pregnancy

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Abstract

Objectives: To evaluate the etiology and outcomes of moderate to severe thrombocytopenia during pregnancy.

Methods: A retrospective study was conducted in pregnant women with moderate to severe thrombocytopenia (platelet count < 100 x 109/L), who were admitted for delivery or termination of pregnancy, at Songklanagarind Hospital; from January 2008 to December 2017.

Results: A total of 138 cases were recruited, with 78.3% being referrals. Immune thrombocytopenia was the most prevalent (44.9%), followed by gestational thrombocytopenia (18.8%), and preeclampsia/HELLP syndrome (12.3%). Postpartum hemorrhage was the most common maternal complication (21.7%). Adverse maternal outcomes were: maternal deaths (1.4%), splenectomy (8%), admission to the intensive care unit (5.8%), and receiving packed red cells > 4 units (10.9%). Adverse neonatal outcomes were abortion (8.7%), low birth weight (35.7%), preterm delivery (33.3%), stillbirth (8.3%), low Apgar score at 5 minutes (13.6%), and neonatal clinical bleeding (2 cases; gastrointestinal bleeding and intraventricular hemorrhage).

Conclusion: Immune thrombocytopenia was the most common cause of moderate to severe thrombocytopenia in our center. Accurate and early diagnosis with appropriate treatment and timely referral are essential to reduce adverse outcomes.

INTRODUCTION

Thrombocytopenia during pregnancy is defined as a platelet count below 150 x 109/L, which may be caused by either an increased destruction or decreased production of the platelet [1-3]. Risk of maternal bleeding is of the most concern. The fetuses are also at risk of neonatal birth asphyxia, neonatal thrombocytopenia and bleeding complications; especially, internal organ hemorrhage and death [4-8].

There are several causes of thrombocytopenia with gestational thrombocytopenia being the most common; accounting for 65-80% of cases [3,9-11]. It is a benign condition with a mild to moderate degree, is not associated with adverse pregnancy outcomes, and does not require any further investigation [3]. Other causes of thrombocytopenia are preeclampsia/ HELLP syndrome (hemolysis, elevated liver enzymes and low platelet count), primary immune thrombocytopenia (ITP), secondary immune thrombocytopenia, association with systemic conditions and congenital thrombocytopenia [3].

The etiologies are varied among studies; for example, studies from Israel [4] and China [8] found gestational thrombocytopenia to be the most common, followed by ITP and preeclampsia, whilst a study from India found gestational thrombocytopenia to be the most prevalent, followed by HELLP syndrome and hepatitis E [7], whereas another study, also from India, reported gestational thrombocytopenia, severe preeclampsia/HELLP syndrome and malaria, respectively [6]. A study from Thailand reported gestational thrombocytopenia to be the most common cause, followed by preeclampsia/HELLP syndrome and ITP, respectively [5]. The differences among studies might be due to population backgrounds as well as context of the study area. The etiology of thrombocytopenia determines both pregnancy outcomes as well as prognosis. In addition, appropriate and timely treatment affect the outcomes. Hence, accurate diagnosis is essential for proper management.

The severity of thrombocytopenia is classified into 3 degrees, based on the levels of the platelet count: mild

thrombocytopenia with a platelet count of 100 x 109/L to less than 150x 109/L, moderate with 50 x 109/L to less than 100 x 109/L, and severe with less than 50 x109/L, respectively [4,12,13]. A mild degree of thrombocytopenia has little impact on clinical outcomes, thus it is of interest to focus on the moderate to severe degrees (platelet count < 100 x 109/L). Data of etiologies and outcomes of moderate to severe thrombocytopenia during pregnancy are, however, limited in our country along with the rest of Southeast Asia. To our knowledge, there has been only one study having been conducted in Thailand, published in the national journal, but it only contained a small sample size (only 65 cases) [5]. In addition, only a few studies used a platelet count of 100 x 109/L as a reference value [4,8]. Therefore, we conducted this study to determine the etiology and outcomes of moderate to severe thrombocytopenia during pregnancy in a tertiary care center in the South of Thailand.

MATERIAL AND METHODS

A retrospective study was conducted including all pregnant women with moderate to severe thrombocytopenia (platelet count < 100 x 109/L), who were admitted for delivery or termination of pregnancy, at Songklanagarind Hospital, a tertiary care center in the South of Thailand; from January 2008 to December 2017. After approval from the Ethics committee of the Faculty of Medicine, Prince of Songkla University (REC.61-049-12-4), data were extracted from the database of the Statistical Unit of the Department of Obstetrics and Gynecology, Faculty of Medicine, Prince of Songkla University as well as from the Hospital Information System of Songklanagarind Hospital. All medical records were reviewed for maternal demographics and clinical data, including: maternal age, parity, underlying medical diseases, a history of thrombocytopenia and treatment, gestational age at diagnosis, referred cases, gestational age at referral, causes of thrombocytopenia based on discharge diagnoses, platelet count during admission for pregnancy termination or delivery, clinical bleeding throughout pregnancy, admission to the intensive care unit, platelet transfusion, blood transfusion and death. The obstetric data were: gestational age at delivery, pregnancy complications, route of delivery, birth weight, Apgar score, neonatal platelet count, bleeding complications in neonates, admission to the neonatal intensive care unit, stillbirth and early neonatal death.

Definition of variables

- Moderate thrombocytopenia: platelet count of 50 x 109/L to less than 100 x 109/L
- Severe thrombocytopenia: platelet count of less than 50 x109/L
- Gestational thrombocytopenia: a benign condition with mild to moderate degrees coupled with an absence of a history of thrombocytopenia, diagnosed by exclusion of other diseases. Platelet count spontaneously returns to normal levels within the first two months postpartum [3].
- Immune thrombocytopenia (ITP), or idiopathic thrombocytopenic purpura: an isolated low platelet count (< 100 x 109/L) in the absence of other causes of thrombocytopenia, [3] characterized by destruction of platelets due to antiplatelet antibodies.
- Preeclampsia: new onset of hypertension (with blood pressure values of 140/90 mmHg or more) and proteinuria, or hypertension and significant end-organ dysfunction, with or without proteinuria, after 20 weeks of gestation, in a previously normotensive woman.
- HELLP syndrome: hemolysis, elevated liver enzymes and low platelet count.
- Secondary immune thrombocytopenia: thrombocytopenia associated with other immune-mediated disorders, such as antiphospholipid syndrome, systemic lupus erythematosus (SLE); infections, such as human immunodeficiency virus (HIV), hepatitis C virus, hepatitis E virus, malaria, Dengue virus, cytomegalovirus, Helicobacter pylori; and drug-induced thrombocytopenia (use of drugs such as heparins, antimicrobials, anticonvulsants, analgesic agents) [3,6].
- Systemic conditions: thrombocytopenia associated with systemic conditions, such as disseminated intravascular coagulation (DIC), splenic sequestration, bone marrow disorders, nutritional deficiencies [3].
- Adverse maternal outcomes: a composite of maternal conditions including any of the following: maternal death, receiving packed red cell transfusion > 4 units, admission to the intensive care unit, or receiving a splenectomy during pregnancy.

Etiologies of thrombocytopenia were categorized into 6 main groups, according to the ACOG Practice Bulletin number 207 as: gestational thrombocytopenia, hypertension in pregnancy (preeclampsia, HELLP syndrome), primary immune thrombocytopenia, secondary immune thrombocytopenia, association with systemic conditions and congenital thrombocytopenia [3].

Statistical analysis

Etiology and outcomes of thrombocytopenia in pregnancy were analyzed using descriptive statistics. SPSS version 17.0 was used for data analysis.

RESULTS

A total of 138 cases were studied. Demographic data and clinical characteristics are shown in Table 1, with most cases in our study being referred from other hospitals. Fifteen cases who had a history of thrombocytopenia from a

previous pregnancy, were diagnosed as: ITP (8), gestational thrombocytopenia (4), preeclampsia (1), SLE (1), and portal hypertension with hypersplenism (1). Three cases, who had a splenectomy before pregnancy, were ITP.

Table 2 shows the etiologies of thrombocytopenia. ITP was the most prevalent, followed by gestational thrombocytopenia and preeclampsia/HELLP syndrome. No congenital thrombocytopenia was noted in our series.

Regarding maternal outcomes (Table 3), a high frequency of cesarean sections was noted, with a previous cesarean section being the most common indication (39.3%), followed by fetal distress (9.8%) and cephalopelvic disproportion (9.1%), respectively. Postpartum hemorrhage was the most common maternal complication. There were two maternal deaths, which occurred due to Evans syndrome with uncorrectable severe anemia and sepsis that ended up with multi-organ failure (1), and ITP with an intracranial hemorrhage (1). A splenectomy was performed during pregnancy in 11 cases, including ITP (10) and Evans syndrome (1), due to medical treatment failure.

For fetal and neonatal outcomes (Table 3), two cases, delivered from mothers with ITP, had clinical bleeding with favorable outcomes. Stillbirths (11 cases) were in mothers with preeclampsia (6), ITP (1), Dengue virus infection (1), autoimmune disease (1), and DIC (2).

Table 4 shows clinical characteristics and adverse pregnancy outcomes of the three most common etiologies: gestational thrombocytopenia, preeclampsia/HELLP syndrome and immune thrombocytopenia. Mothers in the preeclampsia/HELLP syndrome group delivered at the earliest gestational age. Maternal platelet count was the lowest in the ITP group, with the highest rate of severe thrombocytopenia. The highest rate of abruptio placentae was noted in the preeclampsia/HELLP syndrome group.

Table 1

Demographic data and clinical characteristics (N=138)

	N (%)	Median (Min-Max)
Age (years)		31.7 (17-52)
Parity		1 (0-9)
- Nulliparity	61 (44.2)	
- Multiparity	77 (55.8)	
Referred cases	108 (78.3)	
Gestational age at referral		37 (8-41)
Thrombocytopenia in previous pregnancy	15 (10.9)	
Previous splenectomy	3 (2.2)	
Gestational age at diagnosis (weeks)		33.5 (6-41)
Trimester at diagnosis		
- First	25 (18.1)	
- Second	19 (13.8)	
- Third	94 (68.1)	
Platelet count (nadir) (x 10^9/L)		40 (2-99)
Severity of thrombocytopenia (nadir)		
- Moderate degree (50 x 10^9/L to less than 100 x 10^9/L)	62 (44.9)	
- Severe degree (<50 x 10^9/L)	76 (55.1)	
Clinical bleeding	49 (35.5)	
- *Epistaxis/bleeding per gum/ petechiae/ ecchymosis*	*47(34.1)*	
- *Hematuria*	*3 (2.2)*	
- *Gastrointestinal bleeding*	*1 (0.7)*	
- *Intracranial hemorrhage*	*1 (0.7)*	

Table 2

Etiology of thrombocytopenia (N = 138)

Etiology	**N (%)**
Immune thrombocytopenia	62 (44.9)
Gestational thrombocytopenia	26 (18.8)
Preeclampsia/HELLP syndrome	17 (12.3)
Secondary immune thrombocytopenia	
- Autoimmune diseases	15 (10.9)
- Infection	9 (6.5)
Dengue infection	*8*
Malaria	*1*
- Drug-induced	1 (0.7)
Systemic conditions	
- Disseminated intravascular coagulation	3 (2.2)
- Thalassemia diseases with hypersplenism	4 (2.9)
- Portal hypertension with hypersplenism	1 (0.7)

Table 3

Pregnancy outcomes

Pregnancy outcomes	N (%)	Median (min-max)
Outcome of pregnancy		
- Abortion	12 (8.7)	
- Total deliveries	126 (91.3)	
• *Term delivery*	*84/126 (66.7)*	
• *Preterm delivery*	*42/126 (33.3)*	
Route of delivery (N =126)		
• Vaginal delivery	52 (41.3)	
• Cesarean section	74 (58.7)	
Gestational age at delivery (weeks)		38 (25-41)
Maternal complications		
• Postpartum hemorrhage (ml)	30 (21.7)	
• Uterine atony	25 (18.1)	
• Abruptio placentae	7 (5.1)	
• Maternal death	2 (1.4)	
Receiving platelet transfusion (unit)	108 (78.3)	12 (3-68)
Receiving fresh frozen plasma (unit)	48 (34.8)	5.5 (1-63)
Receiving packed red cell transfusion (unit)	94 (68.1)	2 (1-12)
Receiving platelet concentrate ≥ 6 units	82 (59.4)	
Receiving fresh frozen plasma ≥ 4 units	41 (29.7)	
Receiving packed red cell ≥ 4 units	15 (10.9)	
Splenectomy during pregnancy	11 (8.0)	
Intensive care unit admission	8 (5.8)	
Fetal/neonatal outcomes		
Birth weight (g) [N = 123]		2,800 (620-4,372)
Low birth weight (<2,500 g) [N = 123]	46 (35.7)	
Stillbirth [N = 126]	11 (8.3)	
Apgar score at 5 minutes [N = 126]		9 (0-10)
Low Apgar score at 5 minutes (<7) [N = 126]	18 (13.6)	
Neonatal platelet count (x 10^9/L) [N = 73]		212 (11-403)
Neonatal thrombocytopenia [N = 73]	19 (26.0)	
Neonatal intensive care unit admission [N = 115]	24 (20.9)	
Neonatal clinical bleeding [N = 115]		
- Gastrointestinal bleeding	1 (0.9)	
- Intraventricular hemorrhage	1 (0.9)	

Table 4

Clinical characteristics and adverse maternal and neonatal outcomes of thrombocytopenia by different etiologies

	Gestational Thrombocytopenia (N = 26)	Preeclampsia/HELLP syndrome (N = 17)	ITP (N = 62)
Age (years)	33 (19-48)	31.4 (20-46)	31.5 (17-52)
GA at diagnosis (wk)	38 (19-41)	32 (22-38)	30 (6-41)
GA at delivery (wk)	38 (37-41)	32 (25-38)	37 (29-41)
Platelet count (nadir) (x 10^9/L)	82 (50-99)	44 (11-85)	19.5 (2-94)
Severe thrombocytopenia	0%	52.9%	82.3%
Postpartum hemorrhage	7.7%	41.2%	17.7%
Abruptio placentae	0%	23.5%	3.2%
Composite of adverse maternal outcomes	3.8%	23.5%	24.2%
Fetal/neonatal outcomes	N = 26	N = 16	N = 57
Low birth weight	15.4%	85.7%	25.0%
Preterm	0%	75.0%	35.1%
Stillbirth	0%	31.2%	3.5%
Low Apgar score (< 7) at 5 minutes	0%	37.5%	12.3%
Neonatal thrombocytopenia	0% (n = 17)	20.0% (n = 5)	47.4% (n = 38)
Any fetal/neonatal complications	15.4%	93.8%	64.9%

HELLP syndrome: hemolysis, elevated liver enzymes and low platelet count; ITP: immune thrombocytopenia

DISCUSSION

This present study found that there were several etiologies of moderate to severe thrombocytopenia in pregnancy, wherein ITP was the most common cause, followed by gestational thrombocytopenia and preeclampsia/HELLP syndrome. High rates of adverse maternal and fetal outcomes were noted. Postpartum hemorrhage was the most common maternal complications. Two maternal deaths were reported in our series.

Regarding the etiologies of thrombocytopenia in pregnancy, our study showed different results from those of previous studies, which consistently found gestational thrombocytopenia to be the most prevalent [4-8]. This could be explained by our institution being a tertiary care center in the South of Thailand, wherein the most severe cases from 14 provinces in the southern areas are referred to, as demonstrated by the large percentage of referrals in our series. In addition, we recruited only cases with a platelet count below 100 x 109/L, therefore, a large proportion of gestation thrombocytopenia with mild degree were excluded. Other causes of thrombocytopenia were different in order among other studies, most likely due to population backgrounds and the context of the area-based study [4-8].

We found a difficulty in differential diagnosis between severe spectrum of gestational thrombocytopenia and a mild degree of ITP, since both conditions are diagnosed by exclusion. The pathogenesis of gestational thrombocytopenia is still uncertain, possibly resulting from hemodilution, or increased platelet clearance [14]. The key characteristics of gestational thrombycytopenia are: 1) onset most commonly occurs in the mid-second to third trimester; 2) no history of thrombocytopenia outside of pregnancy; 3) not associated with maternal bleeding; 4) platelet count usually >70 x 109/L; 5) spontaneous resolution after delivery, usually within 1-2 months; 6) not associated with fetal thrombocytopenia; 7) may recur in subsequent pregnancies; and 8) no specific test for diagnosis [3,9]. However, some cases were difficult in the making of a diagnosis, especially when platelet counts were around 50 x 109/L – 70 x 109/L. If it occurs in the first trimester, it is usually due to ITP, although gestational thrombocytopenia can occur in early pregnancy, it typically develops later [3]. It has been suggested that a short trial of prednisolone may be useful for diagnosis, concurrent with therapy [15]. In our series, some cases were referred at the time of delivery. The hematologist decided to prescribe corticosteroid or intravenous immunoglobulin without waiting. For gestational thrombocytopenia, most cases in previous studies had a platelet count more than 75 x 109/L [1,11], however, some

cases have been reported to have a platelet count as low as 43 x 109/L [16].

In the secondary immune thrombocytopenia group, most cases were previously diagnosed as autoimmune diseases, with or without treatment with steroids, followed by infections, mainly Dengue fever and one case of malaria. Causes of infection and adverse outcomes were varied among studies [6,7]. For example, a study from India reported a high frequency of maternal death from hepatitis E viral infection (35%) [7], whilst another study, also from India, showed a high rate of malarial infection in their series (11%), resulting in a high stillbirth rate (40%) [6]. Our study demonstrated the serious effects of Dengue viral infection to the fetus, causing stillbirth in 1/8 cases. In the group associated with systemic conditions, we had 4 cases of thalassemia major with hypersplenism. Our area, one of the countries in Southeast Asia, has a high prevalence of thalassemia disease. In our hospital, couples at risk of thalassemia diseases was 2.8% [17].

Regarding maternal outcomes, clinical bleeding occurred in one-third of cases, and 2 cases resulted in death; one (ITP), diagnosed during early pregnancy, with intracranial hemorrhage occurring before arrival, whom was referred from a hospital where platelet concentrate was not available, and the other (Evans syndrome) with treatment failure and sepsis. If we could diagnose and treat both more timely and appropriately, maternal deaths might be preventable. The rates of preterm delivery along with postpartum hemorrhage in our study were higher than previous reports [4-6,8]. Our series also had high rates of platelet transfusions and cesarean sections with a previous cesarean section being the most common indication. To prevent maternal bleeding complications, it was crucial to raise the platelet levels up to 50 x 109/L for cesarean delivery or major surgery, and 70 x 109/L for spinal or epidural anesthesia [3]. A splenectomy was carried out during pregnancy in 8%, which reflected a high number of cases with refractory to medical treatment.

Regarding neonatal outcomes, our study showed high rates of low birth weight, stillbirth, low Apgar scores at 5 minutes and neonatal intensive care unit (NICU) admission, with different rates as compared to previous reports possibly due to the differences in population backgrounds, etiologies, sample size, and severity of diseases [4-8].

Pregnancy outcomes were different based on their etiologies. Accurate diagnosis is essential for specific and timely treatment. For example, in case of preeclampsia/ HELLP syndrome, if termination of pregnancy is delayed, adverse outcomes will occur to both mothers and fetuses. For ITP, spontaneous bleeding, especially in vital organ, may result in death.

The strength of our study was that we had quite a large sample size of moderate to severe degrees of thrombocytopenia cases with complicated conditions in the context of a tertiary care center in the South of Thailand. In addition, adverse outcomes in both mothers and fetuses also seemed to be more prevalent than previous reports [4-6,8].

Some limitations have to be addressed. Our institution is a tertiary care center in the South of Thailand, and seems to have a recruitment bias for the study on etiologies; since most severe cases were referred to our hospital. This could further explain why gestational thrombocytopenia was not the most prevalent, as reported in other previous studies [4-8]. In addition, causes of thrombocytopenia were assigned based on discharge diagnosis by hematologists, however some cases were difficult to differentiate as to the etiology due to an overlap in clinical presentation. As a retrospective study, some data may have been missed, although our data were extracted from the database of the Statistical Unit of our department, which is regularly checked and corrected by both staff members and residents in training monthly via a conference.

CONCLUSIONS

Moderate to severe thrombocytopenia during pregnancy has various etiologies with immune thrombocytopenia being the most common in our center with high rates of adverse pregnancy outcomes. Accurate diagnosis with timely treatment and early referral are essential to reduce adverse outcomes.

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