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ORIGINAL ARTICLE

Severe thrombocytopenia in pregnancy: a case series from west China

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Abstract

Thrombocytopenia is the second most common hematological disease during pregnancy and is mainly caused by gestational thrombocytopenia, immune thrombocytopenia, or preeclampsia/HELLP syndrome. This study aims to investigate the causes and pregnancy outcomes of thrombocytopenia in pregnancies with platelet counts below 50×10^9/L. We retrospectively analyzed the pregnancies diagnosed with severe thrombocytopenia at a tertiary care center in western China between January 2009 and December 2017. All enrolled pregnancies were divided into three groups according to the lowest platelet counts: group A ($30–50\times10^9$/L), group B ($10–30\times10^9$/L), and group C ($<10\times10^9$/L). Maternal and fetal outcomes were observed and compared among these three platelet levels. A total of 533 consecutive pregnancies were included. A relatively large proportion (37.3%, 199/533) of them showed a history of thrombocytopenia before pregnancy or during a previous pregnancy. Most of the women (70.2%, 374/533) received corticosteroids, intravenous immunoglobulin, or platelet transfusion treatments. The incidence of preterm birth < 37 weeks (26.3%, 15/57), cesarean section (93%, 53/57), and neonatal intensive care unit (NICU) admission (31.6%, 18/57) occurred significantly more often in group C than in groups A and B. Neonatal platelet counts were detected in 28.2% of the infants (155/549), and neonatal thrombocytopenia was found in 40.6% of the infants (63/155). Intracranial hemorrhage occurred in 0.9% of the neonates (5/549) throughout the study period, with neonatal nadir platelet counts between 20×10^9/L and 245×10^9/L. One perinatal death occurred in group C. Pregnancies with the lowest platelet counts below 10×10^9/L are more often complicated by preterm birth, cesarean section, and NICU admission compared with those lowest platelet counts $30–50\times10^9$/L and $10–30\times10^9$/L. Neonatal intracranial hemorrhage was uncommon in pregnancies with severe thrombocytopenia. Active management should be performed to avoid possible preterm birth and neonatal NICU admission in pregnancies with the lowest platelet counts below 10×10^9/L.

Keywords Thrombocytopenia · Pregnancy · Platelet count · Adverse pregnancy outcome · Perinatal death

Introduction

Thrombocytopenia is the second most common hematological disease during pregnancy, with an incidence of 5–10% [1]. According to the American College of Obstetricians and Gynecologists (ACOG) guidelines, thrombocytopenia in pregnancy is defined as a platelet count of less than 150×10^9/L [2]. In China, thrombocytopenia in pregnancy is diagnosed with a platelet count below 100×10^9/L [3, 4]. The causes of thrombocytopenia in pregnancy involve multiple physiologic or pathologic conditions, mainly including gestational thrombocytopenia (GT), primary/secondary immune thrombocytopenia purpura (ITP), preeclampsia (PEC)/hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome, and other diseases [1, 2, 5].

GT is benign and usually needs no additional tests or specialized care. Clinical reports suggest that almost all asymptomatic pregnancies with platelet counts between 100×10^9/L and 150×10^9/L are GT or even healthy pregnancy without increased risk of maternal or fetal bleeding complications [3, 4].

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However, some other causes of thrombocytopenia are serious medical disorders, which could result in increased maternal and fetal morbidity, especially when those causes lead to severe thrombocytopenia (platelet counts less than 50×10^9/L) during pregnancy [6]. These pregnancies are also under an increased risk of maternal bleeding, neonatal thrombocytopenia, and even neonatal hemorrhage [7]. ITP is the most common cause of platelet counts below 50×10^9/L during the first and second trimesters [1]. ITP is diagnosed by exclusion, because there are still no pathognomonic symptoms or diagnostic tests specific for ITP [8]. After the exclusion of drug-induced thrombocytopenia and other medical disorders, an isolated platelet count below 50×10^9/L is more suggestive of ITP [3, 4]. Other than ITP, PEC/HELLP syndrome is the most probable cause of severe thrombocytopenia in the late second or third trimesters of pregnancy [1]. PEC/HELLP syndrome is a serious pregnancy complication that harms both the mother and the fetus. The diagnostic criteria and treatment strategies for PEC/HELLP syndrome are complicated [1, 9]. Corticosteroids and intravenous immunoglobulin (IVIg) serve as the first-line treatments for immune thrombocytopenia during pregnancy [8]. Platelet transfusion is mostly used to prepare a thrombocytopenia-affected pregnant woman for delivery [10]. Consensus guidelines recommend that maternal platelet counts above 50×10^9/L are safe for both cesarean section and vaginal delivery [2].

The aim of this study was to investigate the possible causes, treatments, and pregnancy outcomes in pregnancies with the lowest platelet counts below 50×10^9/L and explore the active management strategies.

Materials and methods

Participant selection and data collection

A cross-sectional study was conducted with medical records of pregnancies diagnosed with severe thrombocytopenia from January 2009 until December 2017 in the West China Second University Hospital, the regional tertiary referral center with maternal–fetal medicine specialists, critical care specialists, and maternal and neonatal intensive care units. Approval was obtained from the institutional review board of West China Second University Hospital. All cases of thrombocytopenia in pregnancy were identified through reviewing the medical records of the hospital. Severe thrombocytopenia in pregnancy was diagnosed when platelet counts by a complete blood count (CBC) revealed results lower than 50×10^9/L during pregnancy. Pregnancies that were complicated by pancytopenia or underwent induced abortion were excluded. CBC was performed using a D × H 800 analyzer (Beckman Coulter Inc., San Diego, California, USA). All pregnancies complicated with severe thrombocytopenia got consultation opinions from hematologists. After delivery, all women complicated with severe thrombocytopenia were referred to another hospital with a hematology department.

There is still no available evidence to guide the frequency of platelet counts in pregnancies with severe thrombocytopenia. In most of the included cases, maternal platelet counts were measured before pregnancy, at diagnosis, and on average 5–6 times afterward per patient. In this study, the lowest platelet values throughout the pregnancy and platelet values before and after delivery were used for analysis. Data on maternal demographics (maternal age, gravidity, parity, and ethnicity), medical and obstetric history, treatments, biochemical parameters, and obstetric and bleeding complications during pregnancy and perinatal outcomes were retrieved from the medical records of all included cases of severe thrombocytopenia in pregnancy.

Definitions

A history of thrombocytopenia was positive if platelet levels lower than 100×10^9/L were present at any time before this pregnancy. History of thrombocytopenia in pregnancy was defined as blood platelet levels lower than 100×10^9/L during any previous pregnancy in the same woman. Guidelines suggest that most fatal bleeding has been reported to occur in adults who have platelet counts lower than 30×10^9/L and treatments should be considered [1, 2, 4, 6]. Meanwhile, platelet counts below 10×10^9/L were considered as very serve thrombocytopenia [8, 11]. We divided all included pregnancies into three thrombocytopenia groups according to the lowest platelet counts during pregnancy: group A (platelet levels 30–50×10^9/L), group B (platelet levels 10–30×10^9/L), and group C (platelet levels $<10\times10^9$/L) according to the lowest measured platelet numbers throughout the pregnancy. ITP was diagnosed on the basis of international consensus criteria: Women with an isolated platelet count below 50×10^9/L without any drug-induced thrombocytopenia or other medical disorders [3, 4].

The diagnostic criteria for PEC/HELLP syndrome matched the recommendations by the American College of Obstetricians and Gynecologists [12]. Pregnancy outcomes included gestational age at delivery, postpartum hemorrhage (PPH, defined as blood loss > 1000 mL in cesarean section or > 500 mL in vaginal delivery in the first 24 h after birth) [13], fetal sex, Apgar scores, preterm birth (< 37 weeks and < 34 weeks), mode of delivery (vaginal delivery, cesarean section, and associated anesthesia strategy), birthweight, small for gestational age (defined as birthweight < 10th percentile), meconium staining of the amniotic fluid, intrauterine fetal death, neonatal death, admissions to the neonatal intensive care unit (NICU), neonatal platelet counts, neonatal thrombocytopenia (platelet count $<150\times10^9$/L) [14], and neonatal intracranial hemorrhage.

Statistical analysis

Medians and interquartile range were calculated for continuous variables; differences among groups were analyzed by the nonparametric Kruskal–Wallis test. Numbers and percentages were calculated for categorical variables, and differences among groups were analyzed by the Fisher's exact test. All p values were two-sided, and a p value < 0.05 was considered statistically significant. Statistical analyses were performed with SPSS Statistics 21 software (IBM SPSS Statistics for Windows, NY, IBM Corp.).

Results

Between 2009 and 2017, a total of 595 pregnancies in 570 women with severe maternal thrombocytopenia (platelet counts less than 50×10^9/L) were enrolled in this study. Of them, 62 pregnancies were excluded: 17 cases due to pancytopenia (diagnosed with aplastic anemia by bone marrow biopsy before pregnancy) and 45 cases owing to induced abortion after fully considering the maternal complications and medical conditions. Thus, in this study period, 533 pregnancies in 508 women were included, of whom 95.1% (483/508) had one pregnancy; the other 4.9% (25/508) had two consecutive thrombocytopenia-affected pregnancies and were included as separate cases in this study. Of these 533 pregnancies, 52.5% (280/533) had low maternal platelet counts of $30–50 \times 10^9$/L (group A), 36.8% (196/533) had lower maternal platelet counts of $10–30 \times 10^9$/L (group B), and 10.7% (57/533) had the lowest maternal platelet counts $< 10 \times 10^9$/L (group C).

Baseline characteristics

Maternal age in group C was significantly younger than in groups A and B ($P = 0.000$). The gravidity, parity, and ethnicity demonstrated no statistical differences among the three groups ($P > 0.05$). The number of twin pregnancies showed no significant difference between groups A and B ($P > 0.05$). The number of pregnancies with a history of thrombocytopenia in groups B and C was significantly higher than those in group A ($P = 0.000$). Pregnancies with a history of thrombocytopenia in a previous pregnancy in group C were significantly higher than those in groups A and B ($P = 0.000$). For those pregnancies with thrombocytopenia identified during pregnancy, the gestational age at the diagnosis of thrombocytopenia demonstrated no significant differences among the three groups ($P = 0.276$).

A large number of women (70.2%, 374/533) received treatments during pregnancy or prior to labor. All treatments were given after consulted with a hematologist if they have one of the following clinical indications: symptoms; platelet counts $< 30 \times 10^9$/L at any stage of pregnancy; platelet counts $< 50 \times 10^9$/L in late pregnancy. As for the treatment strategies, corticosteroids and/or IVIG could be used at any stage of pregnancy for women who have symptoms or platelet counts $< 30 \times 10^9$/L. Platelet transfusion was only used to prepare pregnancies for delivery (just before or during vaginal delivery/cesarean section in cases with platelet counts below 50×10^9/L). In this cross-sectional study, platelet transfusion alone (42.5%, 159/374) was the most frequently used therapy in all the included pregnancies with severe thrombocytopenia, followed by corticosteroids combined with platelet transfusion (32.1%, 120/374) and corticosteroids combined with IVIg and platelet transfusion treatment (8.8%, 33/374). We also observed 20 cases (5.3%, 20/374), all in group A, who received only corticosteroid therapy during pregnancy. Corticosteroids combined with IVIg treatment (0.8%, 3/374) and IVIg combined with platelet transfusion (2.7%, 10/374) were seen only in group C. Other therapies, including erythropoietin or Chinese herbal/patent medicine, accounted for 7.8% (29/374) of all the pregnancies with severe thrombocytopenia. Meanwhile, another 29.8% of pregnancies received no treatment in this study; this subset of pregnancies had the lowest platelet count $30–50 \times 10^9$/L at early or mid-trimester of pregnancy without clinical signs of bleeding. Thus, no treatment was subjected to them. Thereafter, during late pregnancy, the platelet levels of this subset were recovered above 50×10^9/L and no treatment were needed before delivery. No side effects of corticosteroids, IVIg, or platelet transfusion treatment were found. Eleven women underwent splenectomy before pregnancy.

All laboratory data of platelet counts 72 h (h) prior to delivery, 24 h after delivery, and the lowest numbers during pregnancy could be retrieved. The maternal platelet counts prior to delivery and the lowest values during pregnancy demonstrated statistically significant differences among the three groups, respectively ($P = 0.000$). However, platelet counts after delivery showed no significant differences among these three platelet levels ($P = 0.225$). The detailed maternal demographics within the study population are given in Table 1.

Causes, maternal bleeding symptom, and maternal outcomes

Considering the causes of severe thrombocytopenia in the included pregnancies, ITP was diagnosed in 92.9% (260/280), 93.4% (183/196), and 75.4% (43/57) of the pregnancies in groups A, B, and C, respectively. PEC/HELLP syndrome accounted for 7.1% (20/280), 6.6% (13/196), and 24.6% (14/57) of the pregnancies in groups A, B, and C, respectively. The proportions of ITP in group A and group B were significantly higher than in group C ($P = 0.000$). The

Table 1 Maternal demographics within the study population

Baseline demographic	Population $N=533$	Platelet counts, $\times 10^9$/L			P
		Group A (30–50) $n=280$	Group B (10–30) $n=196$	Group C (<10) $n=57$	
Maternal age, y[a]	27 (25–32)	26 (24–33)	28 (25–31)	24 (23–29)	0.000[c,d]
Gravidity, n[a]	2 (1–3)	2 (2–3)	2 (1–3)	1 (1–2)	0.063
Parity, n[a]	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0.086
Han nationality, n (%)	514 (96.4%)	268 (95.7%)	192 (98%)	54 (94.7%)	0.269
Twin pregnancy, n (%)	16 (3.0%)	10 (3.6%)	6 (3.1%)	0	0.803
History of thrombocytopenia, n (%)	155 (29.0%)	50 (17.9%)	80 (41.5%)	25 (43.9%)	0.000[b,d]
History of thrombocytopenia in pregnancy, n (%)	44 (8.3%)	17 (6.1%)	13 (6.6%)	14 (24.6%)	0.000[c,d]
Gestational age at diagnosis, d[a,e]	105 (84–182)	119 (84–230)	86 (83–112)	105 (66–141)	0.276
Treatments	374 (70.2%)	160 (57%)	157 (80.1%)	57 (100%)	0.000[b,c,d]
Platelet transfusion, n (%)	159 (42.5%)	83 (51.9%)	59 (37.6%)	17 (29.8%)	0.004[b,d]
Corticosteroids + platelet transfusion, n (%)	120 (32.1%)	21 (13.1%)	76 (48.4%)	23 (40.4%)	0.000[b,d]
Corticosteroids + IVIg + platelet transfusion, n (%)	33 (8.8%)	13 (8.1%)	16 (10.2%)	4 (7.0%)	0.753
Corticosteroids, n (%)	20 (5.3%)	20 (12.5%)	0 (0%)	0 (0%)	–
IVIg + platelet transfusion, n (%)	10 (2.7%)	0 (0%)	0 (0%)	10 (17.5%)	–
Corticosteroids + IVIg, n (%)	3 (0.8%)	0 (0%)	0 (0%)	3 (5.3%)	–
Others, n (%)	29 (7.8%)	23 (14.4%)	6 (3.8%)	0 (0%)	0.020
Prior splenectomy, n (%)	11 (2.1%)	0 (0%)	5 (2.6%)	6 (10.5%)	0.019
Before delivery PLT, $\times 10^9$/L[a]	43 (26–60)	53 (43–65)	27 (21–40)	9 (6–14)	0.000[b,c,d]
After delivery PLT, $\times 10^9$/L[a]	55 (43–76)	61 (47–83)	52 (37–71)	50 (37–60)	0.225
Lowest counts PLT, $\times 10^9$/L[a]	32 (16–43)	42 (37–46)	18 (14–23)	6 (5–8)	0.000[b,c,d]

[a]Values are presented as median (interquartile range); [b]significant difference between groups A and B; [c]significant difference between groups B and C; [d]significant difference between groups A and C; [e]only analyze those cases diagnosed during pregnancy

percentages of PEC/HELLP in group A and group B were significantly lower than in group C ($P=0.000$). The data are shown in Table 2.

Maternal mucosal and/or cutaneous hemorrhage was observed in 73.7% (393/533) of the pregnancies; 52.1% (146/280) and 96.9% (190/196) of the pregnancies exhibited mucosal and/or cutaneous bleeding in group A and group B, respectively. All pregnancies in group C (57/57) exhibited mucosal and/or cutaneous bleeding during pregnancy. The occurrence of mucosal/cutaneous bleeding in groups B and C was significantly higher than in group A ($P=0.000$). No maternal visceral or intracranial hemorrhage was observed in this study cohort (Table 2).

Pregnancies in groups A, B, and C showed no statistically significant differences of gestational age at delivery ($P=0.122$). Preterm birth at <37 weeks was found more often in group C (26.3%) than in group A (11.8%) and group B (13.8%) ($P=0.021$). Of these preterm labor cases, 27.3% (9/33), 11.1% (3/27), and 20% (3/15) in groups A, B, and C, respectively, were spontaneous preterm birth, and all the remains were iatrogenic preterm labor due to obstetric complications, including placental previa, premature rupture of fetal membranes (PROM), or placental abruption. Meanwhile, the incidence of preterm birth at <34 weeks demonstrated no statistically significant differences among groups A (3.2%, 9/280), B (1.0%, 2/196), and C (5.3%, 3/57) ($P=0.104$). All instances of preterm labor before 34 weeks of gestation were iatrogenic, mainly due to PEC/HELLP. In this study, 423 pregnancies (79.4%) underwent cesarean section, of which 210 cases (75%) were in group A, 160 cases (81.6%) in group B, and 53 cases (93.0%) in group C ($P=0.004$); 90.1% (381 cases) of these cesarean deliveries were performed with general anesthesia, with the general anesthesia rates in group B (96.3%) and C (100%) significantly higher than in group A (82.9%) ($P=0.000$). The percentages of PPH in groups A, B, and C also demonstrated no significant difference ($P=0.568$). In addition, meconium-stained amniotic fluid rates were comparable among groups A (4.6%), B (3.6%), and C (3.5%) ($P=0.901$) (Table 2).

Neonatal pregnancy outcomes

No statistically significant differences were found in newborn sex among the three groups ($P=0.183$). Two cases

Table 2 Causes, maternal bleeding symptom, and maternal outcomes within the study population

	Population $n=533$	Thrombocytopenia, PLT, $\times 10^9$/L			P
		Group A (30–50) $n=280$	Group B (10–30) $n=196$	Group C (<10) $n=57$	
Diagnosis of ITP, *n* (%)	486 (91.2%)	260 (92.9%)	183 (93.4%)	43 (75.4%)	0.000[c,d]
Diagnosis of PEC/HELLP, *n* (%)	47 (8.8%)	20 (7.1%)	13 (6.6%)	14 (24.6%)	0.000[c,d]
Mucosal/cutaneous bleeding, *n* (%)	393 (73.7%)	146 (52.1%)	190 (96.9%)	57 (100%)	0.000[b,d]
Maternal visceral or intracranial hemorrhage, *n* (%)	0	0	0	0	–
Gestational age at delivery, *d*[a]	271 (262–275)	272 (263–276)	270 (263–275)	264 (254–273)	0.122
Preterm birth <37 wk, *n* (%)	75 (14.1%)	33 (11.8%)	27 (13.8%)	15 (26.3%)	0.021[d]
Spontaneous, *n* (%)	15 (20%)	9 (27.3%)	3 (11.1%)	3 (20%)	0.298
ITP, *n* (%)	13 (86.7%)	7 (77.8%)	3 (100%)	3 (100%)	–
PEC/HELLP, *n* (%)	2 (13.3%)	2 (22.2%)	0	0	–
Iatrogenic, *n* (%)	60 (80%)	24 (72.7%)	24 (88.9%)	12 (80%)	0.298
ITP, *n* (%)	17 (28.3%)	4 (16.7%)	11 (45.8%)	2 (16.7%)	–
PEC/HELLP, *n* (%)	43 (71.7%)	20 (83.3%)	13 (54.2%)	10 (83.3%)	–
Preterm birth <34 wk, *n* (%)*	14 (2.6%)	9 (3.2%)	2 (1.0%)	3 (5.3%)	0.104
Mode of delivery					
Vaginal delivery, *n* (%)	110 (20.6%)	70 (25%)	36 (18.4%)	4 (7.0%)	0.004[d]
Cesarean section, *n* (%)	423 (79.4%)	210 (75%)	160 (81.6%)	53 (93.0%)	0.004[d]
General anesthesia, *n* (%)	381 (90.1%)	174 (82.9%)	154 (96.3%)	53 (100%)	0.000[b,d]
Intraspinal anesthesia, *n* (%)	42 (9.9%)	36 (17.1%)	6 (3.7%)	–	0.000
Postpartum hemorrhage, *n* (%)	20 (3.8%)	8 (2.9%)	7 (3.6%)	3 (5.3%)	0.568
Meconium-stained amniotic fluid, *n* (%)	22 (4.1%)	13 (4.6%)	7 (3.6%)	2 (3.5%)	0.901

[a]Values are presented as median (interquartile range); [b]significant difference between groups A and B; [c]significant difference between groups B and C; [d]significant difference between groups A and C

*All cases were iatrogenic preterm birth due to PEC/HELLP

(0.4%) of newborns had Apgar scores at 5 min < 7: 1 case (0.4%) in group A and 1 case (1.8%) in group C ($P=0.310$). Neonate birthweights manifested no significant differences among the three groups ($P=0.171$), and no differences were seen in the percentages of small-for-gestational-age neonates among group A, group B, and group C ($P=0.872$). Neonatal NICU admission occurred in 56 cases (10.5%, 56/533) of all the pregnancies, with the highest percentage in group C (31.6%, 18/57) ($P=0.000$). NICU admission occurred in 12 cases (4.3%) in group A: 11 cases complicated by ITP and 1 case complicated by PEC/HELLP. Twenty-six cases of NICU admission were observed in group B: 23 cases complicated by ITP, followed by 3 cases diagnosed with PEC/HELLP syndrome. Of the 18 cases of NICU admission in group C, 9 cases were complicated by PEC/HELLP, and the other 9 cases were accompanied by ITP (Table 3).

Of 155 neonates (28.2%) in whom cord platelet counts were tested, 63 neonates' platelet counts (40.6%) were below 150×10^9/L. The neonatal platelet count detection rates in group C were significantly higher than in group A and group B ($P=0.000$). Neonatal platelet levels showed no significant differences among the three platelet count levels (P = 0.543). Neonatal thrombocytopenia rates were not different among groups A (37.5%), B (42.0%), and C (42.1%) ($P=0.892$). Intracranial hemorrhage occurred in 5 neonates (0.9%) in the study: 2 cases (0.7%) in group A (nadir platelet counts 20×10^9/L and 245×10^9/L), 2 cases (1.0%) in group B (nadir platelet counts 23×10^9/L and 63×10^9/L), and one case (1.8%) in group C (nadir platelet count 195×10^9/L) ($P=0.527$). One intrauterine fetal death (1.8%) was observed in group C, a 23-year-old woman (gravida 2, para 1) whose pregnancy was complicated by a dead intrauterine fetus at 36^{+2} gestational weeks, whose platelet counts prior to delivery and after delivery were 5×10^9/L and 51×10^9/L. No neonatal death occurred in this study population. In addition, 11 women underwent splenectomy before this pregnancy. Of these 11 pregnancies, neonates from 9 cases were admitted to the NICU, and 5 neonates complicated with neonatal thrombocytopenia. The detailed information is shown in Table 3.

Table 3 Neonatal outcomes within the study population

	Population $n=533$	Thrombocytopenia, PLT, $\times 10^9$/L			P
		Group A (30–50) $n=280$	Group B (10–30) $n=196$	Group C (<10) $n=57$	
Fetal sex (male), *n* (%)	297 (54.1%)	166 (56.8%)	106 (53.0%)	25 (43.9%)	0.183
Apgar scores at 5 min < 7, *n* (%)	2 (0.4%)	1 (0.4%)	0	1 (1.8%)	0.310
Birthweight, *g*[a]	3050 (2600–3370)	3190 (2600–3450)	3020 (2800–3280)	2940 (2410–3300)	0.171
Small for gestational age, *n* (%)	25 (4.7%)	14 (5%)	8 (4.1%)	3 (5.3%)	0.872
NICU admission, *n* (%)	56 (10.5%)	12 (4.3%)	26 (13.3%)	18 (31.6%)	0.000[b,c,d]
ITP, *n* (%)	43 (76.8%)	11 (91.7%)	23 (88.5%)	9 (50%)	0.005[c,d]
PEC/HELLP, *n* (%)	13 (23.2%)	1 (8.3%)	3 (11.5%)	9 (50%)	0.005[c,d]
No. of neonatal platelet counts, *n* (%)*	155 (28.2%)	48 (16.6%)	69 (34.2%)	38 (66.7%)	0.000[b,c,d]
Neonatal platelet levels, $\times 10^9$/L[a]	210 (110–265)	216 (157–266)	215 (98–271)	197 (17–242)	0.543
Neonatal thrombocytopenia, *n* (%)[e]	63 (40.6%)	18 (37.5%)	29 (42.0%)	16 (42.1%)	0.892
Neonatal intracranial hemorrhage, *n* (%)*	5 (0.9%)	2 (0.7%)	2 (1.0%)	1 (1.8%)	0.527
Intrauterine fetal death, *n* (%)*	1 (0.2%)	0	0	1 (1.8%)	–
Neonatal death, *n* (%)	0	0	0	0	–
Prior splenectomy, *n* (%)	11 (2.1%)	0	5 (2.6%)	6 (10.5%)	0.019
NICU admission, *n* (%)	9 (81.8%)	0	4 (80.0%)	5 (83.3%)	–
Neonatal thrombocytopenia, *n* (%)	5 (45.5%)	0	2 (40.0%)	3 (50.0%)	–

[a]Values are presented as median (interquartile range); [b]significant difference between groups A and B; [c]significant difference between groups B and C; [d]significant difference between groups A and C; [e]neonatal platelet counts lower than 150×10^9/L

*Data were calculated based on the numbers of neonates

Discussion

This relatively large cross-sectional study analyzed the baseline characteristics, treatment strategy, and perinatal outcomes of pregnancies complicated by severe thrombocytopenia. Our results demonstrated significantly increased risks of preterm birth before 37 weeks of gestation and neonatal NICU admission when the lowest platelet counts were below 10×10^9/L during pregnancy.

It has been widely noticed that thrombocytopenia in pregnancy might lead to maternal bleeding, neonatal thrombocytopenia, and even neonatal hemorrhage [7]. The most commonly seen maternal bleeding included subcutaneous ecchymosis, bruising, purpura, and gingival bleeding [4, 7, 15]. In this study cohort, mucosal and/or cutaneous hemorrhage was observed in almost all pregnancies with platelet counts below 30×10^9/L, as well as in half of the pregnancies with nadir platelet counts in the range of $30–50\times 10^9$/L. However, no maternal visceral or intracranial hemorrhage was observed. The absence of severe bleeding complications in our data was consistent with previous reports [7].

The PPH rate in this cohort (3.8%) was comparable to those reported in previous large population studies (3–6%) [16, 17]. However, the non-increased PPH rate was in contrast to another national cohort study (51% of PPH and 21% of severe PPH were reported) [7]. The distinct study population, different management strategies, and therapeutic effects during pregnancy might have contributed to this discrepancy. In this study cohort, among the 20 cases of PPH, three cases were complicated by placental previa, and one case had uterine leiomyoma. No identifiable risk factors for PPH were found in the remaining 16 cases. The correlation between severe thrombocytopenia and PPH remains to be explored.

In this study population, over 90% of severe thrombocytopenia cases in pregnancy were diagnosed with ITP. Treatment options for ITP during pregnancy are restricted to corticosteroids, IVIg, and platelet transfusion. Corticosteroids and IVIg could be used during pregnancy to enhance the platelet counts [18]. Platelet transfusion is mostly suitable for the delivery period because the effect of transfused platelets is reported to be short [15]. In this study, 100% and 80.1% of pregnancies with the lowest platelet counts below 10×10^9/L and in the range of $10–30\times 10^9$/L, respectively, received treatments, which complied with guideline recommendations (treatment was needed in pregnancies with platelet counts less than 30×10^9/L at any stage of pregnancy or below 50×10^9/L in late pregnancy) [6]. Moreover, platelet transfusion is the most used strategy to prepare the pregnant women for delivery. The usage of platelet transfusion

also proved to conform to the consensus (just before or during vaginal delivery/cesarean section in cases with platelet counts below 50×10^9/L) [10]. Meanwhile, corticosteroids combined with IVIg could enhance the platelet counts to safe levels in immune thrombocytopenia [18] and were used in 32.1% of the cases in this study. Our results were also in consistent with another literature, around 80% ITP during pregnancy were undergone treatment, and a small proportion of ITP need no treatment during pregnancy [7].

PEC/HELLP is a serious pregnancy complication that harms both the mother and fetus. Thrombocytopenia is one of the typical clinical manifestations; the treatment of low platelet counts resulting from PEC/HELLP should focus on treatment of the causative diseases [19]. In this cross-sectional study, PEC/HELLP accounted for 8.8% in pregnancies complicated with severe thrombocytopenia, which is much higher than general obstetric population (2.35–2.89%) [20, 21]. Seventy-nine percent of women in this study were delivered by cesarean section per obstetric indications or by maternal demand. It had been reported that the cesarean section rate in the general obstetric population is 41.1–45.6% between 2012 and 2016 in our country [22]. Most of the included pregnancies in this cross-sectional study had superimposed complications other than severe thrombocytopenia. The indications of cesarean section in this cross-sectional study are placental factors (placenta previa, placental implantation), fetal factors (fetal distress, fetal macrosomia, and abnormal presentation), and maternal factors (heart disease, severe preeclampsia, scarred uterus, and pelvic abnormality). The decision of cesarean section is a comprehensive consideration for the safety of both mother and fetus. For maternal safety, 90.1% of these cesarean sections were performed with general anesthesia, the other 9.9% with intraspinal anesthesia. As for general obstetric population, all non-emergency cesarean sections without high-risk factors (such as thrombocytopenia and spinal deformity) should be performed with intraspinal anesthesia. The anesthesia strategies implemented in this cross-sectional study were complied with the guidelines [6]. General anesthesia is safe for severe thrombocytopenia because invasive procedure-related bleeding risk could be avoided. Due to the appropriate management of severe thrombocytopenia by the maternal–fetal medicine specialists, no increased risk of bleeding complications with anesthesia or delivery was seen in this study.

Moreover, a higher incidence (14.1%) of women delivering before 37 weeks of gestation was seen in pregnancies with platelet counts below 50×10^9/L, as opposed to the overall national preterm birth rate in East Asia of 7.2% [23]. More important, the occurrence of preterm birth in pregnancies with platelet counts below 10×10^9/L (26.3%) was significantly higher than in those pregnancies with platelet counts in the range of $10–30\times10^9$/L or $30–50\times10^9$/L. Thrombocytopenia itself is not an indication for terminating the pregnancy or delivering by cesarean section [2]. The optimal gestational age or mode of delivery should be determined by obstetric conditions. However, the causes leading to low platelet levels or other concurrent complications might result in iatrogenic preterm labor. After reviewing the medical records of pregnancies complicated by preterm labor in this study cohort, 20% (15/75) were spontaneous preterm births, and the other 80% (60/75) were iatrogenic preterm births due to obstetrical indications. In another study on the treatment of ITP (platelet counts below 100×10^9/L) in pregnancy, preterm labor < 37 wk were found in 8.5–9.8% pregnancies after treatment [18]. The rate of preterm births was reported to be as high as 18.5% in a study with 30 cases of ITP in pregnancy [24].

In addition, the occurrence of NICU admission increased with decreased maternal platelet counts; 31.6% of neonates were admitted to the NICU from pregnancies with platelet counts below 10×10^9/L. Half of them were complicated by ITP, and the other half were accompanied by PEC/HELLP. ITP and PEC/HELLP are two predominant causes for platelet counts below 10×10^9/L and may lead to adverse fetal outcomes. In pregnancies with platelet counts of $10–30\times10^9$/L and $30–50\times10^9$/L, the NICU admission rate was 13.3% and 4.3%, respectively. Iatrogenic preterm birth due to obstetric indications, spontaneous preterm birth, jaundice, and pneumonia was responsible for these NICU admissions. In another national cohort study, neonatal NICU admissions were reported in 7% of pregnancies complicated with severe ITP [7].

It has been reported that ITP could affect fetuses because maternal antiplatelet IgG may cross the placenta and place the fetus/neonates at high risk of thrombocytopenia [6, 24]. Thus, invasive fetal sampling or procedures should be avoided in neonates born from severe ITP pregnancies; cord platelet counts were performed for 155 neonates (28.2%). This reflects that obstetricians and neonatologist in our hospital have not paid enough attention to the possible neonatal thrombocytopenia in ITP mothers. Most of them (66.7%) were from pregnancies with platelet counts below 10×10^9/L. Sixty-three cases (40.6%) proved to have neonatal thrombocytopenia, which is slightly higher than those reported in ITP pregnancies (14–37%) [6, 7, 25]. Meanwhile, neonatal intracranial hemorrhage occurred in only 5 cases with neonatal nadir platelet counts of $20–245\times10^9$/L. Of them, four cases were complicated by ITP and the other one was accompanied by PEC/HELLP. This confirms the reports that fetal/neonatal intracranial hemorrhages are uncommon in pregnancies with severe thrombocytopenia [25].

This study also found that a history of thrombocytopenia before pregnancy or during a previous pregnancy was present more frequently when the lowest platelet counts were below 10×10^9/L. Thus, obstetricians should be cautious

with adverse pregnancy outcomes in these history-positive pregnancies. Active management of thrombocytopenia to enhance the maternal platelet levels to normal may benefit both mother and fetus. Women of childbearing age with severe thrombocytopenia should receive special care and continuous monitoring before and during pregnancy. Studies suggest that the preparation for pregnancy should be reasonably postponed for women with platelet counts $< 30 \times 10^9$/L [25]. Most of the severely thrombocytopenia-affected pregnancies had concurrent pregnancy complications. Thus, the adverse maternal and neonatal outcomes could not rule out the potential effects from these complications.

Pregnancies with the lowest platelet counts below 10×10^9/L are at higher risks of preterm birth and NICU admission compared with those lowest platelet counts $10–30 \times 10^9$/L and $30–50 \times 10^9$/L. ITP and PEC/HELLP are the most commonly seen causes for severe thrombocytopenia during pregnancy. Pregnancies complicated by severe thrombocytopenia should be managed with appropriate therapies on a case-by-case basis to avoid possible adverse pregnancy outcomes.

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Compliance with ethical standards

Conflict of interests The authors have no conflicts of interest in this paper.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. For this type of study, formal consent was not required.

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