Thrombocytopenia in pregnancy with different diagnoses
Differential clinical features, treatments, and outcomes
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Abstract
To investigate the clinical features and perinatal treatment of thrombocytopenia induced by different causes during pregnancy.
Clinical data from 195 pregnant women with thrombocytopenia attending 2 tertiary hospitals from January 2014 to October 2016 were retrospectively studied. The obtained data were analyzed with SPSS 19.0 software.
There were 117 (60.0%), 55 (28.2%), and 23 cases (11.8%) of pregnancy-associated thrombocytopenia (PAT), idiopathic thrombocytopenia (ITP), and hypertensive disorder in pregnancy (PIH), respectively. The percentage of nulliparous women, gestational age at delivery, date of diagnosis of thrombocytopenia, and delivery mode significantly differed between the patients in these 3 groups ($P < .05$). Patients with PIH had a higher percentage of premature delivery and of lower birth weight infants than patients in the other 2 groups. The 3 groups had similar incidences of postpartum hemorrhage, rates of stillbirth, and neonatal Apgar scores at 5 minutes. PAT and PIH patients had different platelet counts after delivery compared with at diagnosis, whereas the platelet counts of the ITP patients were similar at diagnosis and after delivery. ITP patients in the nontreatment group and the treatment group had significantly different platelet counts ($P < .05$), and in the treatment group, the maternal platelet count did not differ for treatment with intravenous immunoglobulin (IVIg) versus corticosteroids.

The causes of thrombocytopenia in pregnancy are diverse, and the clinical features vary widely. Timely analysis is needed to determine the primary cause of thrombocytopenia, and appropriate therapy should then be selected to effectively improve the prognosis of pregnancies.

Abbreviations: ITP = idiopathic thrombocytopenia, IVIg = intravenous immunoglobulin, PAT = pregnancy-associated thrombocytopenia, PIH = hypertensive disorder in pregnancy

Keywords: pregnancy, thrombocytopenia, treatment differential

1. Introduction
Thrombocytopenia is one of the most common hematologic complications of pregnancy and is caused by diverse factors. The most common type is pregnancy-associated thrombocytopenia (PAT), which accounts for 65% to 80% of the cases,\textsuperscript{1} followed by idiopathic thrombocytopenia (ITP) and hypertensive disorder in pregnancy (PIH). Other less common causes of thrombocytopenia in pregnancy include coagulopathy related to sepsis/disseminated intravascular coagulation (DIC), microangiopathic hemolytic anemia with thrombotic thrombocytopenic purpura and kidney injury; however, these cases were not detected in our study population. Severe thrombocytopenia in pregnancy increases the risk of postpartum hemorrhaging, neonatal asphyxia, and neonatal thrombocytopenia. PAT is currently considered a benign disease,\textsuperscript{2} but its diagnosis remains primarily a matter of exclusion; therefore, a differential diagnosis is of particular importance. In contrast, mothers with typical ITP often have more severe thrombocytopenia, and the treatment options for ITP in pregnancy remain limited. Both corticosteroids and intravenous immunoglobulin (IVIg) are acceptable treatments for ITP in pregnancy, but studies that compare the efficacy of these 2 common treatments to select the initial treatment are rare. Therefore, guidance regarding the selection of an appropriate treatment based on the different causes of thrombocytopenia in pregnancy is urgently needed; however, the differentiation between PAT and ITP remains a diagnostic challenge. Previous studies have discovered that the time of onset of thrombocytopenia and patients’ platelet counts are the strongest predictors of ITP for pregnant women.\textsuperscript{3} In this study, we examined the early clinical predictors of ITP and methods to distinguish it from PAT and PIH. Additionally, regarding PIH, which is one of the most common causes of thrombocytopenia in pregnancy, moderate or severe thrombocytopenia can also be observed in partial PIH patients. The clinical features that distinguish PIH from other causes of thrombocytopenia during pregnancy and the associated therapies for thrombocytopenia during pregnancy are limited and rarely reported.
Based on the findings above, a protocol for the clinical prediction and early diagnosis of the potential causes of thrombocytopenia during pregnancy is urgently needed. In this retrospective study, the clinical features of the different causes of thrombocytopenia in pregnancy were investigated. The treatment and prognosis of these different causes were also analyzed among pregnancies complicated with thrombocytopenia.

2. Patients and methods

2.1. Study design and patients

This was a retrospective study of pregnant patients with thrombocytopenia attending 2 tertiary hospitals from January 2014 to October 2016. This study was approved by the Institutional Review Board (IRB) of the 2 hospitals and was performed in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent before enrolment in this study. A total of 13,286 pregnant women visited our hospitals during the study period. Women were eligible for the study if they had 2 platelet counts lower than 100,000/μL during their pregnancy. Patients were excluded from the study if they had any of the following: multiple gestations, missing platelet counts before treatment, at delivery or postpartum, or irregular examinations during pregnancy. Ultimately, a total of 195 pregnant women were enrolled in our study. Data were extracted from patients’ medical records, hospital computerized databases, or clinical charts by means of a questionnaire.

2.2. Study definition

The inclusion criteria for patients included pregnancy with a diagnosis of ITP or pregnancy with a previous history of ITP, defined as ITP in pregnancy[13] PAT was defined as a healthy pregnant woman who had no history of thrombocytopenia, was first diagnosed with thrombocytopenia during the gestation period, had negative maternal platelet-associated immunoglobulin G and had no other positive clinical targets after assessments, such as bone marrow cytomorphologic examination and coagulation function test; normalization of platelet count within 12 weeks of treatment further confirmed the diagnosis. PIH was diagnosed according to the definition in Obstetrics and Gynaecology,[15] which defines PIH as new-onset hypertension with blood pressure values of 140/90 mmHg or more and 24 hours proteinuria of 0.3 g or more that occurs after 20 weeks of gestation. Patients with preexisting medical disorders such as hypertension, diabetes mellitus, heart disease, and renal disease and patients with connective tissue disorders were excluded. Patients who had a platelet count less than 30 × 10^9/L or a tendency to bleed received active treatment. Corticosteroid treatment referred to oral prednisolone (1 mg/kg/day for 5–7 days) or intravenous dexamethasone (20 mg/day for 3–5 days). Intravenous immunoglobulin (IVlg) (400 mg/kg/day for 5 days) was administered when there was an inadequate response to corticosteroid treatment and was also used as an initial therapy in some patients. Patients who received corticosteroids, IVlg, or both treatments during the pregnancy and perinatal period were included in the treatment group, and other patients, including those who received blood transfusions, were included in the nontreatment group.

2.3. Statistical analysis

All data were statistically analyzed using commercially available statistical software (SPSS 19.0; IBM Corp., Armonk, NY). Continuous variables were compared using Student t test, 1-way ANOVA, or the Brown-Forsythe test for independent samples. Categorical variables were evaluated using Pearson Chi-squared test or Fisher exact test as appropriate. The correlation between maternal platelet count at delivery and the nadir neonatal platelet count was evaluated by Pearson correlation analysis. All tests were bilateral, and a P-value < .05 was considered statistically significant. The results were expressed as the mean ± standard deviation (SD) for continuously distributed variables and percentages and frequencies for categorical variables.

3. Results

3.1. Maternal and neonatal characteristics

During the study period, 195 pregnancies complicated with thrombocytopenia were identified. Of the patients enrolled, 117 cases (60.0%) were caused by PAT, 55 cases (28.2%) by ITP, and 23 cases (11.8%) by PIH. The mean age of these patients was 28.3 ± 4.2 years (21–40 years). At enrollment, the mean platelet count was 59.6 ± 23.8 × 10^9/L and ranged from 10 × 10^9/L to 98 × 10^9/L.

### Table 1

| Variables                  | PAT (n=117) | ITP (n=55) | PIH (n=23) | All groups | PAT vs ITP | PAT vs PIH |
|----------------------------|-------------|------------|------------|------------|------------|------------|
| Maternal age, y            | 28.1 ± 4.2  | 27.2 ± 3.4 | 30.6 ± 3.8 | .012 < .05 | .752 < .008 | .008 < .05 |
| Times of pregnancy         | 2.2 ± 1.3   | 1.5 ± 0.7  | 1.9 ± 1.1  | .001 < .05 | .000 < .05 | .255 < .05 |
| Gestational age, wk        | 38.0 ± 2.4  | 37.1 ± 2.4 | 35.5 ± 2.9 | .000 < .05 | .045 < .05 | .002 < .05 |
| Date of diagnosis of thrombocytopenia |           |            |            |            |            |            |
| Before 12 wk of pregnancy  | 3 (2.5)     | 55 (100.0) | 3 (13.0)   | .000 < .05 | .000 < .05 | .008 < .05 |
| 12–28 wk of pregnancy      | 78 (66.7)   | 0 (0.0)    | 8 (34.8)   | .000 < .05 | .000 < .05 | .000 < .05 |
| After 28 wk of pregnancy   | 36 (30.8)   | 0 (0.0)    | 12 (52.2)  | .000 < .05 | .000 < .05 | .000 < .05 |
| Vaginal delivery/cesarean section | 46/69       | 14/41      | 1/22       | .001 < .05 | .047 < .05 | .001 < .05 |
| Postpartum hemorrhage (n)  | 4 (3.4)     | 3 (3.6)    | 1 (4.3)    | 1.000 < .05 | 1.000 < .05 | 1.000 < .05 |
| Premature delivery         | 23 (19.7)   | 17 (30.9)  | 14 (60.9)  | .000 < .05 | .103 < .000 | .000 < .05 |
| Stillbirth                 | 4 (3.4)     | 2 (3.6)    | 3 (13.0)   | .215 < .05 | .047 < .05 | .001 < .05 |
| Apgar scores at 5 min      | 9.5 ± 1.9   | 9.5 ± 1.9  | 8.0 ± 3.4  | .005 < .05 | .142 < .000 | .000 < .05 |
| Neonatal birth weight, g   | 3135.3 ± 610.6 | 2366.5 ± 655.6 | 2376.9 ± 882.4 | .005 < .05 | .142 < .000 | .000 < .05 |

ITP = idiopathic thrombocytopenia, PAT = pregnancy-associated thrombocytopenia, PIH = hypertensive disorder in pregnancy.

*P < .05.
in Table 1. The percentage of nulliparous women, gestational age at delivery, date of diagnosis of thrombocytopenia, and delivery mode significantly differed between the patients in these 3 groups (all \( P < .05 \)). Thrombocytopenia occurred significantly earlier in women with ITP than in women with PAT and PIH (\( P = .000 \)). Gestational age at delivery was significantly lower in women with PIH and ITP than in those with PAT (all \( P < .05 \)). More PAT patients delivered vaginally than ITP and PIH patients (41.0% vs 25.5% and \( P = .047 \); 41.0% vs 4.3% and \( P = .001 \), respectively). PIH patients had significantly higher percentages of premature and low birth weight infants than women in the other 2 groups (all \( P < .05 \)). The incidence of postpartum hemorrhaging, rate of stillbirth and neonatal Apgar scores at 5 minutes were similar among the 3 groups (all \( P > .05 \)). None of the newborns showed any signs of hemorrhagic diathesis, and there were no cases of neonatal death in the 3 groups.

The platelet count at initial presentation, delivery day, and postpartum day 2 were significantly lower in women with ITP than in those with PAT and PIH (all \( P < .05 \)). Additionally, the platelet counts of the PAT and PIH patients were significantly higher 48 hours after delivery than at diagnosis (\( P = .001 \) and \( P = .047 \), respectively), whereas the platelet counts of ITP patients at diagnosis and after delivery were similar (45.04 ± 20.52 vs 44.87 ± 20.22, \( P = .830 \)) (Table 2). Patients with PAT, ITP, and PIH were all divided into 3 groups according to platelet counts of 50 × 10^9/L to 100 × 10^9/L, 20 × 10^9/L to 50 × 10^9/L, and <20 × 10^9/L (Table 3). Twenty-seven (23.1%) PAT patients and 9 (39.1%) PIH patients required therapy to increase their platelet counts, and the treatment group and nontreatment group of PAT and PIH patients had similar platelet counts 7 days after delivery (\( P = .309 \) and \( P = .816 \), respectively). Of the ITP patients, 43 (78.2%) received therapy during pregnancy, whereas 15 still required therapy to raise their platelet counts in the first few days after giving birth. There was a significant difference in platelet counts 7 days after delivery between the treatment group and nontreatment group (\( P = .049 \)). In the treatment group of ITP patients, 11 pregnant women (25.6%) were treated with more than one administration of corticosteroids and 23 cases (53.5%) with IVlg, whereas 9 patients (20.9%) with severe thrombocytopenia received both treatments. Platelet counts of more than 50 × 10^9/L were more prevalent in patients treated with prednisone as the initial agent than in those treated with IVlg as the initial agent; however, no significant differences were observed between the 2 treatment groups (72.7% vs 56.5%, \( P = .465 \)). Of the pregnant women treated with IVlg at any point during gestation, including combination therapy using IVlg, adverse events were reported in only 2 (4.2%) and included hemolytic anemia in 1 (2.1%) and headache in 1 (2.1%). In addition, neither patient required specific intervention. Of the pregnant women treated with corticosteroids at any point during gestation, adverse events were reported in 4 (8.2%), including hyperglycemia requiring treatment in 3 (6.1%) and infection in 1 (2.0%).
weeks of pregnancy, including 45 women with ITP before pregnancy. The platelet count at diagnosis was 45.04 ± 20.52 × 10^9/L. In addition, 42 patients (76.4%) with ITP had a platelet count of less than 50 × 10^9/L, and this percentage was significantly higher among ITP patients than in PAT patients (20.5%). Thrombocytopenia in PIH is mainly due to vascular endothelial ischemia and hypoxia caused by vascular vasospasm; vascular viscosity increases with damaged endothelial cells, thereby increasing permeability and accelerating platelet aggregation and consumption. The severity of thrombocytopenia is usually closely related to that of the underlying disease. Severe thrombocytopenia in PIH should be distinguished from that due to ITP. Most women with PIH are primigravida and younger than 20 or older than 30 years old; additionally, they account for 17.6% of the maternal deaths in the United States. A majority of these pregnant women require timely termination of their pregnancy according to their obstetric situation, and this situation results in a high proportion of preterm birth and cesarean sections. Maayan-Metzger et al. conducted a retrospective study of 723 pregnant women with thrombocytopenia and verified this conclusion. In the present study, higher percentages of premature delivery and low birth weight infants were observed in the PIH group than in the other 2 groups.

The outcomes of pregnancies with thrombocytopenia have mainly been analyzed by considering postpartum hemorrhaging and neonatal thrombocytopenia. Pregnant women with thrombocytopenia, especially those with severe thrombocytopenia, are at a high risk of postpartum hemorrhaging. In the present study, the rate of postpartum hemorrhage was 3.6%, which was lower than previously reported rates and might be related to the administration of effective treatment before termination of pregnancy in patients with severe thrombocytopenia or a tendency for bleeding. Another reason is that most patients with severe thrombocytopenia have normal coagulant activity. In our study, postpartum hemorrhaging occurred in 7 women due to obstetric factors, including 4 cases of uterine inertia, 2 of placental abruption, and 1 of placenta previa. This result indicated that we should take good care of pregnant women with thrombocytopenia and search for a specific cause of this condition. The timely treatment of primary disease and complications can effectively reduce adverse pregnancy outcomes. Neonatal thrombocytopenia was identified in 9 cases (8 mothers with ITP and 1 with PIH). None of these neonates

Table 3

| Primary disease | Treatment | Total no. of pregnancies | Platelet count (7 d after delivery) | P | Treatment vs nontreatment |
|-----------------|-----------|--------------------------|--------------------------------------|---|--------------------------|
| PAT (n=117)     | No treatment | 90                       | <50; 50–100; >100                      |    |                          |
|                 | Corticosteroids | 14                       | 5; 6; 7                              |    |                          |
|                 | Mg | 4                       | 1; 2; 1                              | .410 | .309                     |
|                 | Corticosteroids and Mg | 9                       | 3; 5                                  |    |                          |
| ITP (n=55)      | No treatment | 12                       | 8; 4; 0                              |    |                          |
|                 | Corticosteroids | 11                       | 3; 7; 1                              | .029 | .049                     |
|                 | Mg | 23                      | 10; 9; 4                             |    |                          |
|                 | Corticosteroids and Mg | 9                       | 1; 3; 5                              |    |                          |
| PIH (n=23)      | No treatment | 14                       | 2; 4; 8                              | .934 | .816                     |
|                 | Corticosteroids | 6                        | 1; 1; 4                              |    |                          |
|                 | Mg | 3                       | 0; 0; 3                              |    |                          |

ITP = idiopathic thrombocytopenia, IVIg = intravenous immunoglobulin, PAT = pregnancy-associated thrombocytopenia, PIH = hypertensive disorder in pregnancy.

I. P < .05.
showed bleeding symptoms or a tendency for bleeding. No correlation was observed between the maternal platelet count at delivery and the neonatal platelet count, and this lack of association was in accordance with research by Hachisuga et al., who also concluded that the presence of a first-born sibling with neonatal thrombocytopenia was a reliable risk factor for neonatal thrombocytopenia in subsequent pregnancies.

The treatment options for thrombocytopenia in pregnancy are limited and are mainly determined by clinical experience. PAT and PIH patients in the nontreatment group and the treatment group showed no significant difference in platelet counts ($P > .05$). The platelet count after delivery was greater than that during pregnancy. Careful blood pressure assessments and regular examination of platelet counts are highly important in these patients, as blood transfusions could be effective in elevating patients’ platelet count before termination of the pregnancy. Evidence to guide management decisions for pregnant patients with ITP is lacking. In our study, among ITP patients, the nontreatment group and the treatment group had significantly different platelet counts ($P < .05$). Sun et al. conducted a retrospective study of 235 pregnancies using blood samples to compare the effectiveness of treatment with IVIg to that of treatment with corticosteroids in pregnancy; these authors concluded that the maternal platelet count response and neonatal outcomes of IVIg and corticosteroids did not differ in pregnant women with ITP. Our data were consistent with their report, as the outcomes of IVIg and corticosteroids did not differ in pregnant women and their offspring.

Thus, a working knowledge of the clinical features and management of pregnant women with thrombocytopenia due to different causes is important for hematologists. Specific therapies, if promptly administered, may significantly improve the outcomes of pregnant women and their offspring.

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