Passive Immune Thrombocytopenia in Neonates of Mothers with Idiopathic Thrombocytopenic Purpura: Incidence and Risk Factors

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ABSTRACT The aim of this study was to evaluate risk factors for occurrence of neonatal passive immune thrombocytopenia (PIT) in pregnancy complicated by idiopathic thrombocytopenic purpura (ITP). We studied 63 pregnant women with ITP and the 66 neonates retrospectively. Neonatal platelet counts were compared with maternal platelet counts, platelet-associated gamma G immunoglobulin (PAIgG) values, and the presence of antiplatelet antibody in the maternal circulation, history of previous PIT, maternal treatments for ITP, and other maternal or neonatal factors. PIT (platelet counts <100 \( \times \) \( 10^3 \)/\( \mu \)L) was observed in 9 (14.3%) of 63 pregnancies. Presence of circulating antiplatelet antibody in maternal blood, splenectomy prior to pregnancy, and history of previous PIT were observed more frequently with statistical significance in patients giving birth to neonates who developed PIT. No effect on occurrence of PIT was found by the administration of corticosteroids or immunoglobulin. Splenectomy prior to pregnancy was found by logistic regression analysis to be a single significant variable (p = 0.021, odds ratio 7.20, confidence intervals: 1.35 to 38.3) among the risk factors for PIT.

Keywords: Idiopathic thrombocytopenic purpura, autoimmune thrombocytopenia, antiplatelet antibody, splenectomy, pregnancy

ITP is a relatively common disease in women of reproductive age. In ITP-complicated pregnancy, the active transport of antiplatelet antibodies through the placenta may cause fetal or neonatal PIT and, at worst, may increase the risk for neonatal intracranial hemorrhage (ICH). However, among infants of mothers with ITP,

Objectives
Upon completion of the article, the reader should be able to 1) know the association of maternal idiopathic thrombocytopenia (ITP) and neonatal passive immune thrombocytopenia (PIT), 2) summarize the treatment options, and 3) identify the important risk factors for PIT.

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Disclosure
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neonatal ICH has been identified at a very low incidence of 0 to 2.3%, and many investigators have favored vaginal delivery unless cesarean section is obstetrically indicated. There is considerable controversy regarding the issue of whether or not it is possible to predict which neonate will be thrombocytopenic. Direct measurement of fetal platelet count is not widely used, because fetal blood sampling by cordocentesis has small but significant risks of morbidity and mortality, especially in the thrombocytopenic fetus. Fetal scalp sampling also is technically difficult, and an inaccurate platelet count can often be obtained by contaminations with maternal blood and sample clotting.

In previous studies, we have demonstrated that the presence of circulating antiplatelet antibodies, splenectomy prior to pregnancy, and history of previous PIT are risk factors for the occurrence of PIT. The current study was designed to investigate the predictive value of a variety of maternal and neonatal factors for the occurrence of PIT by assessing a larger number of pregnant women with ITP.

**MATERIAL AND METHODS**

Sixty-three consecutive ITP patients and their 66 neonates, including three sets of twins, who were born from January 1983 to October 1998 in Hokkaido University Hospital were enrolled in this retrospective study. The diagnosis of ITP was made on the basis of thrombocytopenia (platelet count < 100 × 10^3/μL), the presence of normal or increased numbers of megakaryocytes in the bone marrow without splenomegaly or leukopenia, and laboratory findings such as a positive test for circulating antiplatelet antibodies and PAIgG. Neonatal PIT was diagnosed when a platelet count of the peripheral blood at birth was less than 100 × 10^3/μL. If the platelet count at birth was less than 50 × 10^3/μL, severe PIT was diagnosed. Circulating antiplatelet antibodies were detected by the method of platelet suspension immunofluorescence test (PSIFT). Maternal PAIgG was measured by the ELISA method. The data are presented as nanograms IgG per 10^7 cells (normal, 9.0 to 25.0 ng IgG/10^7 cells).

We investigated the relationship between the occurrence of PIT and various maternal factors, including platelet counts, concentrations of PAIgG, presence of antiplatelet antibodies, history of previous PIT, maternal treatment for ITP, and other various maternal and neonatal factors including gestational age and birth weight. Maternal treatment for ITP consisted of splenectomy prior to pregnancy, prednisolone and high-dose immunoglobulin plus splenectomy prior to pregnancy, prednisolone alone, high-dose immunoglobulin, and no medication.

Statistical analysis was performed by Mann-Whitney U test. Regression analysis for continuous variables, Fisher’s exact test for categoric variables, and logistic regression analysis for multivariables were also performed. A p value less than 0.05 was assumed to be statistically significant.

**RESULTS**

Maternal and neonatal characteristics of the subjects are shown in Table 1. Of the 66 neonates, 9 (13.6%) developed PIT and 5 had severe thrombocytopenia. No ICH was found in any neonate by either ultrasound or neurological examinations. Four neonates with severe PIT required administration of high-dose immunoglobulin or corticosteroids, or both, and the high-dose immunoglobulin was effective in only 1 (case 2) of the 4 cases (Table 2).

By regression analysis, no relationship was found between neonatal platelet counts and maternal platelet counts (p = 0.200) (Fig. 1). No statistical difference of maternal platelet counts, gestational age, neonatal birth weight between mothers with PIT (153 ± 129 × 10^3/μL, 36.8 ± 3.8 weeks of gestational age, 2400 ± 856 g) and mothers without PIT (103 ± 70 × 10^3/μL, 37.5 ± 1.8 weeks of gestational age, 2787 ± 494 g) was observed.

**TABLE 1. Maternal and Neonatal Characteristics**

<table>
<thead>
<tr>
<th>Maternal or Neonatal Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age</td>
<td>29.0 ± 4.8 (18–40) years old</td>
</tr>
<tr>
<td>Primipara</td>
<td>50.8%</td>
</tr>
<tr>
<td>Maternal PAIgG (n = 38)</td>
<td>52.8 ± 49.3 (8.3–215.1) ng/10^7 cell</td>
</tr>
<tr>
<td>Antiplatelet antibody (n = 49)</td>
<td>16.3%</td>
</tr>
<tr>
<td>Maternal platelet count</td>
<td>110 ± 81 (21–368) × 10^3/μL</td>
</tr>
<tr>
<td>Gestational week at delivery</td>
<td>37.4 ± 2.1 (27–41)</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>39.7%</td>
</tr>
<tr>
<td>Birth weight</td>
<td>2698 ± 592 (520–3770) g</td>
</tr>
<tr>
<td>SGA neonate</td>
<td>14.3%</td>
</tr>
<tr>
<td>Cord blood PAIgG (n = 23)</td>
<td>45.8 ± 44.0 (11–172) ng/10^7 cell</td>
</tr>
<tr>
<td>Neonatal platelet count</td>
<td>219 ± 97 (22–424) × 10^3/μL</td>
</tr>
<tr>
<td>PIT</td>
<td>9 (14.3%)</td>
</tr>
</tbody>
</table>

SGA, small-for-gestational-age. Mean ± SD (range)
Maternal concentrations of PAIgG were not related to neonatal platelet counts by regression analysis ($p = 0.174$) (Fig. 2). Of 49 women who were examined by PSTFT, 9 tested positive for circulating antiplatelet antibodies at least once during pregnancy. The prevalence of PIT in women with a positive test was significantly higher than it was in women with negative tests ($p < 0.05$) (Table 3). The sensitivity of PSTFT for detection of PIT was 44.4%, and the specificity was 90.0%. The positive predictive value was 50.0%, and the negative predictive value was 87.5%.

The six treatment groups for maternal ITP and their corresponding prevalence of PIT are shown in Table 4. The prevalence of PIT was significantly higher in patients with splenectomy prior to pregnancy (4/8) than it was in patients without splenectomy (5/55) ($p < 0.05$).

In 30 multipara women we compared the prevalence of PIT between patients with (n = 6) and without a history of PIT (n = 24). Patients with a history of PIT had repeated PIT, with higher prevalence than in patients without the history (66.7% versus 4.2%, $p < 0.01$).

In order to assess the value of each risk factor for PIT we performed logistic regression analysis for variables, including maternal platelet counts, presence of antiplatelet antibodies, administration of corticosteroids, high-dose immunoglobulin and splenectomy prior to pregnancy.

$$\times 10^3 / \mu L$$

![Graph](image_url)

**FIG. 1.** Correlation between maternal and neonatal platelet counts.

### TABLE 2. Characteristics of PIT Patients

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Gestational Week</th>
<th>Delivery Mode</th>
<th>Birth Weight (g)</th>
<th>Platelet Count ($\times 10^3/\mu L$)</th>
<th>Neonatal Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38</td>
<td>C</td>
<td>2255 (SGA)</td>
<td>22</td>
<td>Ig + corticosteroids</td>
</tr>
<tr>
<td>2</td>
<td>39</td>
<td>C</td>
<td>3770</td>
<td>27</td>
<td>Ig</td>
</tr>
<tr>
<td>3</td>
<td>37</td>
<td>C</td>
<td>2050 (SGA)</td>
<td>31</td>
<td>Ig + corticosteroids</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>V</td>
<td>2580</td>
<td>34</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>V</td>
<td>2840</td>
<td>57</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>37</td>
<td>V</td>
<td>2610</td>
<td>68</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>27</td>
<td>C</td>
<td>520 (SGA)</td>
<td>76</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>37</td>
<td>C</td>
<td>2580</td>
<td>89</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>37</td>
<td>V</td>
<td>2395</td>
<td>24</td>
<td>Ig</td>
</tr>
</tbody>
</table>

C, cesarean section; V, vaginal delivery; SGA, small-for-gestational-age
pregnancy, and other maternal and neonatal factors, including gestational age and birth weight. A history of previous PIT or PAIgG was not included as a variable; otherwise, 33 or 25 cases would be lost in the analysis. As a result, splenectomy prior to pregnancy was found as the only significant variable (p = 0.021), with an odds ratio of 7.20 (confidence intervals, 1.35 to 38.3). The other maternal and neonatal factors, including maternal platelet counts, gestational age, birth weight, presence of antiplatelet antibodies, administration of corticosteroids, or high-dose immunoglobulin, were found not to be a significant variable.

**DISCUSSION**

We found no correlation between maternal and neonatal platelet counts. Our data were also in good agreement with previous authors in finding no correlation between maternal concentrations of PAIgG and fetal platelet counts, although other studies did find correlations between these variables. Many investigators have suggested that indirect IgG antibodies might help to identify which neonates of mothers with ITP would have severe thrombocytopenia.

We also observed a higher prevalence of PIT in patients who tested positive at least once for circulating antiplatelet antibodies than we did in patients who consistently tested negative by PSIFT. The detection of circulating antiplatelet antibodies in maternal serum might indicate a risk of occurrence of PIT. However, as found in this study, both the specificity and the sensitivity of PIT prediction by PSIFT were relatively low. Recent studies showed that circulating antiplatelet antibodies directed against platelet membrane glycoprotein IIb/IIIa, Ib/IX, and Ia/IIa might be more useful to distinguish ITP from gestational thrombocytopenia and might be helpful in detecting the increased risk for PIT.

In multipara patients, we found that patients with a history of PIT had a higher prevalence (66.7%) of recurrence than patients without the history had (4.2%). Other investigations on siblings from mothers with ITP revealed the concordant conclusion, showing a significant positive correlation of platelet counts between the siblings. Thus, the platelet count of the first baby may be useful for the management of the next pregnancy complicated by ITP.

High-dose intravenous immunoglobulin therapy in a pregnant woman with ITP was effectively performed
for the first time in 1983. We treated 24 patients with a total of 100 to 222.5 g of intravenous immunoglobulin. Excluding 1 patient who concomitantly received platelet infusions, 10 of 23 patients (43.5%) responded to the therapy with an increase of more than 50 × 10^9/μL in their platelet counts. Maternal administration of corticosteroids and intravenous immunoglobulin were once thought to decrease the prevalence of PIT. In a recent randomized prospective trial on antenatal treatments with low-dose corticosteroids, however, neonatal thrombocytopenia was not prevented. Corticosteroids may even promote transplacental passage of antiplatelet antibodies. The influence of high-dose immunoglobulin therapy on fetal PIT has been assumed to be the following: (1) a transplacental effect that increases the concentration of IgG and platelet counts in fetal blood through active transport of IgG and (2) an immunosuppressive effect that reduces production of antiplatelet antibodies. However, our previous and other studies have reported no significant increase of fetal IgG concentration after maternal infusion of more than 100 g of immunoglobulin and unchanged amounts of maternal PAIgG before and after the infusion. Others also have shown no benefit in increasing fetal platelet counts.

Our current results failed to find any relation between corticosteroids or intravenous immunoglobulin treatment and occurrence of PIT. In this study, 5 (18.5%) of 27 patients who received preclonisolone and 4 (16.7%) of 24 patients who received high-dose immunoglobulin had PIT. The prevalence of PIT in the group of preclonisolone alone and in the group of immunoglobulin alone were 15.4 and 10.0%, respectively. Neither group was significantly different from the group with no medication or from the overall prevalence (14.3%). Thus, no effect on occurrence of PIT was found by the administration of corticosteroids or immunoglobulin.

In this study, four neonates with severe PIT required administration of high-dose immunoglobulin, but the high-dose immunoglobulin was effective in only one case. Two of the other three cases subsequently received corticosteroids and responded well to the treatment. Similarly, it was found that high-dose immunoglobulin was less effective than corticosteroids were in PIT, although some studies reported efficacy of immunoglobulin in the neonatal period.

Splenectomy prior to pregnancy was found to be the single significant factor for PIT among various maternal and neonatal factors by logistic regression analysis, which was also found by other authors. Splenectomy possibly increases free antiplatelet antibodies in the maternal sera, which can pass the placenta because of the removal of the immune complex destruction site. Titer of transferable antiplatelet antibodies might have increased in our patients with splenectomy prior to pregnancy. An alternative explanation for the increased risk of PIT in patients with splenectomy is that the severity of ITP, a corticosteroid-resistant condition that required splenectomy treatment, is itself associated with the increase in high prevalence of PIT. In a mild status of ITP at sustained remission, the risk for the PIT might be very low. Actually, a very low prevalence of PIT in a no medication group (4.8%) was observed in this study. This was also found by other authors. The disease activity itself might be associated with higher risk of PIT.

In order to further understand the mechanism of PIT, a highly sensitive method for measurement of specific antiplatelet antibodies should be developed.

### REFERENCES


