

FETAL ALLOIMMUNE THROMBOCYTOPENIA

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ABSTRACT

Background Alloimmune thrombocytopenia is a serious fetal disorder resulting from platelet-antigen incompatibility between the mother and fetus. The diagnosis is usually made after the discovery of unexpected neonatal thrombocytopenia. Approximately 10 to 20 percent of affected fetuses have intracranial hemorrhages, one quarter to one half of which occur in utero. We studied the correlates of thrombocytopenia in affected fetuses.

Methods We studied 107 fetuses with alloimmune thrombocytopenia at a mean (\pm SD) gestational age of 25 ± 4 weeks, before their entry into one of three treatment protocols. The fetuses were initially evaluated because an older sibling had been given this diagnosis at birth. We compared the initial platelet counts in utero in these 107 fetuses with the platelet count at birth and the history of intracranial hemorrhage in the affected sibling.

Results The initial platelet count was $\leq 20,000$ per cubic millimeter in 53 of the 107 fetuses (50 percent), including 21 of 46 fetuses (46 percent) studied before 24 weeks of gestation. The 97 fetuses with PI^{A1} incompatibility had more severe thrombocytopenia than the 10 fetuses with other antigen incompatibilities. Among seven fetuses with platelet counts of more than 80,000 per cubic millimeter that were not treated initially, the counts decreased by more than 10,000 per cubic millimeter per week. Although 41 fetuses had initial platelet counts that were lower than those measured at birth in an older affected sibling, only a history of antenatal intracranial hemorrhage in the sibling predicted greater severity of thrombocytopenia in the fetus. Only one treated fetus had an intracranial hemorrhage, and the thrombocytopenia resolved after birth in all cases.

Conclusions Fetal alloimmune thrombocytopenia occurs early in gestation, is severe, and is more severe in fetuses with an older affected sibling who had an antenatal intracranial hemorrhage. (N Engl J Med 1997;337:22-6.)

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INCOMPATIBILITY between parental platelet antigens may result in fetal and neonatal alloimmune thrombocytopenia.^{1,2} The most frequent cause of this disorder is a polymorphism affecting the PI^A (HPA-1) antigen, which results from a change from cytosine to thymine at position 196 of the gene for platelet glycoprotein IIIA. This causes the substitution of proline for leucine at amino acid 33 of the protein.³ Alloimmune thrombocytopenia occurs when the antiplatelet antibodies of a sensi-

tized PI^{A1-} mother cross the placenta and cause thrombocytopenia in a PI^{A1+} fetus.^{1,2}

Alloimmune thrombocytopenia occurs in approximately 1 in 1000 neonates. The diagnosis is made after birth, after the discovery of unexpected, severe thrombocytopenia, which is usually identified as a result of signs of bleeding such as petechiae and ecchymoses.⁴⁻⁶ The chief complication is intracranial hemorrhage, which occurs in approximately 10 to 20 percent of affected neonates,⁵⁻⁷ of whom 25 to 50 percent have intracranial hemorrhage in utero.⁸

Overall, the subsequent fetuses of sensitized PI^{A1-} mothers have an 85 to 90 percent chance of having alloimmune thrombocytopenia.³ If the father is heterozygous (PI^{A1}/PI^{A2}), the recurrence rate is 50 percent, whereas if the father is homozygous for PI^{A1} , the recurrence rate is 100 percent.

Because of the relatively high risk of antenatal intracranial hemorrhage, subsequent fetuses found to have alloimmune thrombocytopenia by serologic testing and cordocentesis (fetal-blood sampling) have been enrolled in antenatal treatment protocols designed to increase their platelet counts and thereby reduce the risk of intracranial hemorrhage.⁹⁻¹³ These protocols have included the administration of intravenous immune globulin or glucocorticoids to the mother. The results of two treatment studies have been reported,¹⁰⁻¹² and a third study is still ongoing.

The purpose of this report is to describe the results of the initial, pretreatment blood sampling in 107 fetuses with alloimmune thrombocytopenia enrolled in protocols coordinated at our institutions since 1984. The thrombocytopenia in the fetuses was compared with the clinical characteristics and course of the disorder in their older untreated siblings.

METHODS**Fetuses**

We analyzed data on 107 fetuses enrolled in three multicenter studies of the antenatal management of alloimmune thrombocytopenia¹⁰⁻¹² (Table 1). The studies were approved by the Food and Drug Administration and the appropriate institutional review committees, and informed consent was obtained from the mothers. The details of the protocols, including administration of intravenous immune globulin or glucocorticoids to the mothers, the timing of repeated fetal-blood sampling, and monitoring of

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the effects of treatment, differed from study to study. The first 17 fetuses were described by Lynch et al. in 1992.¹¹ The results of the second trial of 55 fetuses were reported in 1996.¹² Data on 27 fetuses from our ongoing study in which the initial blood sample was obtained before March 1, 1996, are also included in this report. Eight other fetuses underwent blood sampling but were not included in these trials.¹⁴ The characteristics of these 107 fetuses (serial platelet counts defining response to treatment, presence or absence of intracranial hemorrhage, birth weights, and neonatal courses) have been described in previous reports.

Ninety-seven of the 107 cases of alloimmune thrombocytopenia were a result of PI^{A1} (HPA-1a) incompatibility (Table 1). The other 10 cases included 4 with Bak^a (HPA-3a) incompatibility, 2 with Br^a (HPA-5b) incompatibility, 1 with HLA incompatibility, 1 with incompatibility of a recently described platelet antigen,¹⁵ and 2 with an undetermined incompatibility. In more than 85 of the cases, the platelet-typing and antibody-detection studies were performed at the Blood Center of Southeastern Wisconsin.

In the case of all but 2 of the 107 fetuses, the mother was enrolled in the study because she had had an affected child. In the case of these two fetuses, the mother was identified during her first pregnancy because she had a sister whose neonate had been given a diagnosis of alloimmune thrombocytopenia. In the case of seven of the fetuses, the platelet count at birth was not available for the older affected sibling, because the sibling had died in utero (two fetuses) or the mother had more than one affected fetus enrolled in the studies, and we used the platelet count at the birth of the first untreated sibling only once (five fetuses). There were therefore 98 affected siblings who could be evaluated. However, the initial platelet count of each fetus was included separately in the description of fetal thrombocytopenia.

Platelet counts at birth and cranial imaging studies of the older affected sibling were performed as part of the clinical care of these neonates with thrombocytopenia and not as a part of any study. This information was subsequently obtained by our center as part of the antenatal-treatment protocols; the parents' consent for treatment included permission to obtain this information.

Fetal-Blood Sampling

Except when antenatal hemorrhage had occurred in an older sibling, cordocentesis was performed before any treatment was begun. Under ultrasonographic guidance, a 20- or 22-gauge spinal needle was directed through the anterior abdominal wall of the mother into an umbilical vessel.¹⁶ Then, 1 to 3 ml of blood was removed to determine the fetal platelet count; erythrocyte size was used to confirm that the blood was fetal in origin. The timing of this procedure varied as a result of many factors, such as the times of diagnosis and referral.

Statistical Analysis

Chi-square analysis, correlation coefficients, and t-tests were used to analyze the results. All statistical tests were two-tailed.

RESULTS

Time of Onset and Severity of Fetal Thrombocytopenia

The initial platelet counts for each fetus before treatment are shown in Figure 1. Fifty-three of the 107 fetuses (50 percent) had an initial platelet count of $\leq 20,000$ per cubic millimeter, including 21 of the 46 fetuses (46 percent) studied before 24 weeks of gestation, and 75 (70 percent) had platelet counts of $\leq 50,000$ per cubic millimeter. Only four fetuses had normal platelet counts at the time of the initial blood sampling.¹⁷ PI^{A1} incompatibility resulted in more severe fetal thrombocytopenia than did incompatibility for other platelet antigens: the median initial platelet

TABLE 1. CHARACTERISTICS OF 107 FETUSES WITH ALLOIMMUNE THROMBOCYTOPENIA.*

CHARACTERISTIC	ANTIGEN INCOMPATIBILITY		ALL FETUSES
	PI ^{A1}	OTHER	
First fetal-blood sample			
No. of fetuses	97	10	107
Platelet count ($\times 10^{-3}/\text{mm}^3$)			
Mean	35 \pm 36	71 \pm 49	38 \pm 39
Median	18	60	23
Gestational age (wk)			
Mean	25 \pm 4	25 \pm 3	25 \pm 4
Median	24	25	25
First sample obtained <24 wk of gestation			
No. of fetuses	42	4	46
Platelet count ($\times 10^{-3}/\text{mm}^3$)			
Mean	40 \pm 45	79 \pm 58	43 \pm 46
Median	21	65	26
Sample obtained at birth			
No. of infants	88	10	98
Platelet count ($\times 10^{-3}/\text{mm}^3$)			
Mean	25 \pm 21	23 \pm 20	25 \pm 21
Median	20	17	20
Older sibling with intracranial hemorrhage			
No. of fetuses	18	2	20
Initial platelet count ($\times 10^{-3}/\text{mm}^3$)			
Mean	30 \pm 30	65 \pm 36	33 \pm 31
Median	17	65	24
Mean gestational age (wk)	24 \pm 4	28 \pm 2	24 \pm 4
Older sibling without intracranial hemorrhage			
No. of fetuses	70	8	78
Initial platelet count ($\times 10^{-3}/\text{mm}^3$)			
Mean	37 \pm 39	72 \pm 53	41 \pm 42
Median	20	60	25
Mean gestational age (wk)	26 \pm 4	25 \pm 3	26 \pm 4

*Data on 77 of the 107 fetuses have been reported previously.^{11,12,14} Plus-minus values are means \pm SD.

count was 18,000 per cubic millimeter in the 97 fetuses with PI^{A1} incompatibility, as compared with 60,000 per cubic millimeter in the 10 fetuses with other antigen incompatibilities ($P=0.04$) (Table 1).

Changes in Platelet Counts in Untreated Fetuses

Of eight fetuses that were not treated initially, seven had platelet counts of more than 80,000 per cubic millimeter. In these fetuses, the counts fell by more than 10,000 per cubic millimeter per week, as revealed by repeated fetal-blood sampling two to eight weeks later. In the four fetuses with PI^{A1} incompatibility, high initial platelet counts, and no initial treatment, the platelet count decreased by an average of 23,000 per cubic millimeter per week. In the other fetus with PI^{A1} incompatibility, the initial and follow-up counts were very low (Fig. 2). These fetuses were all subsequently treated.

Predicting the Course of a Fetus on the Basis of the Course of an Older Affected Sibling

Forty-one of 98 fetuses (42 percent) had initial platelet counts that were lower than those measured at birth in an older affected sibling, even though the

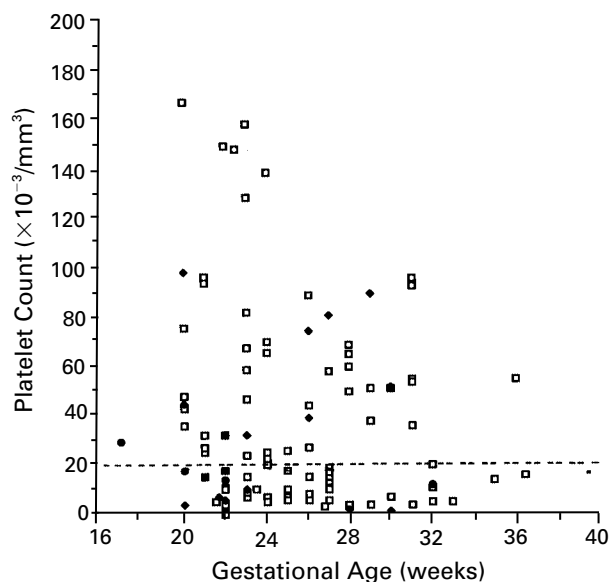


Figure 1. Initial Platelet Count as a Function of Gestational Age in 107 Fetuses with Alloimmune Thrombocytopenia.

Diamonds denote fetuses with an older affected sibling who had had a perinatal intracranial hemorrhage, circles fetuses with an older affected sibling who had had an antenatal intracranial hemorrhage, and open squares fetuses with an older affected sibling who had not had an intracranial hemorrhage. Where solid squares appear, a circle or diamond overlaps an open square. Fifty percent of the platelet counts were $\leq 20,000$ per cubic millimeter (broken line).

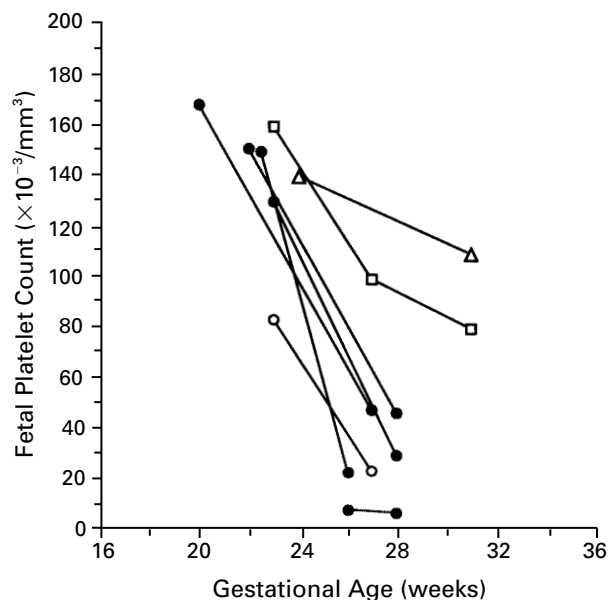


Figure 2. Serial Platelet Counts in Eight Initially Untreated Fetuses with Alloimmune Thrombocytopenia.

The solid circles denote fetuses with Pl^{A1} incompatibility, the squares a fetus with Br^a incompatibility, the triangles a fetus with Bak^a incompatibility, and the open circles a fetus with an undetermined antigen incompatibility.

platelet counts were determined at a mean gestational age of 25 weeks. There was no correlation between the initial platelet counts of the fetuses and the counts of the older affected siblings ($r=0.02$), nor was there a significant difference in the initial platelet counts of the fetuses when the platelet counts of the siblings were grouped according to the severity of thrombocytopenia (Table 2). There was also no correlation between the gestational age at the time of initial sampling and the platelet count of the older affected sibling, excluding the possibility that fetal-blood sampling had been performed later in gestation in fetuses with less severely affected siblings.

Twenty fetuses had an older affected sibling who had had an intracranial hemorrhage. The mean initial platelet count in these 20 fetuses was 33,000 per cubic millimeter (median, 24,000 per cubic millimeter) at a mean gestational age of 24 weeks. These platelet counts did not differ significantly from the values in the 78 fetuses whose older affected siblings had not had intracranial hemorrhage; in those 78 fetuses the mean and median initial platelet counts were 41,000 per cubic millimeter and 25,000 per cubic millimeter, respectively, at a mean gestational age of 25 weeks. However, the five fetuses with older affected siblings who had had an antenatal intracranial hemorrhage had significantly lower initial platelet counts (mean, 18,000 per cubic millimeter; median, 16,000 per cubic millimeter; $P=0.002$).

Outcomes in the Treated Fetuses

Only one of the treated fetuses had an intracranial hemorrhage; this fetus had an older affected sibling who had also had an intracranial hemorrhage in utero. Follow-up of the treated fetuses (the oldest is now 12 years old) has revealed normal growth and development.

DISCUSSION

This study of fetuses with alloimmune thrombocytopenia demonstrates that thrombocytopenia often occurs early in gestation and usually is severe. Fetal thrombocytopenia is more severe in cases of Pl^{A1} incompatibility than with incompatibility of other antigens. In the absence of intervention, the platelet count tends to fall or remain very low. Although thrombocytopenia is often more severe in subsequent fetuses of a sensitized mother, our findings indicate that unless there is a history of antenatal intracranial hemorrhage in the older sibling, the platelet count of the fetus cannot be predicted. These findings have implications for the approach to antenatal treatment of alloimmune thrombocytopenia.

In the 107 fetuses in this study, the thrombocytopenia associated with Pl^{A1} incompatibility was more severe than that associated with incompatibility of other platelet antigens. Although Br^a incompatibility in neonates has been reported to result in less se-

vere thrombocytopenia than PI^{A1} incompatibility,¹⁸ there are fewer data on antigens other than PI^{A1} . Therefore, the results of this study cannot be generalized to cases of alloimmune thrombocytopenia other than those caused by PI^{A1} incompatibility.

In cases of paternal heterozygosity, amniocentesis will allow identification of the platelet-antigen genotype of the fetus.¹⁹ If the fetus does not have the incompatible platelet antigen, the fetus will be unaffected and fetal-blood sampling is unnecessary. But in cases in which amniocentesis demonstrates the fetus to have platelet-antigen incompatibility and in cases of paternal homozygosity, cordocentesis should be performed to determine the initial fetal platelet count. Because there appears to be an increased risk of hemorrhage during cordocentesis in fetuses with severe thrombocytopenia,¹⁴ we recommend transfusion of maternal platelets at the time of fetal-blood sampling to minimize this risk.^{12,20}

The course of an older affected sibling did not help to distinguish which fetus would have severe thrombocytopenia early in gestation, unless the older sibling had had an antenatal intracranial hemorrhage. Herman et al. reviewed 10 cases of antenatal intracranial hemorrhage and suggested that fetuses with an older affected sibling who had had an antenatal intracranial hemorrhage were at greater risk for antenatal hemorrhage.⁸ The relatively high rate of fetal and neonatal intracranial hemorrhage described here (20 of 98 untreated older affected siblings) and in previous reports^{7,8,21,22} is consistent with the early onset and severity of fetal alloimmune thrombocytopenia.

Even in the approximately 95 percent of fetuses whose older affected siblings had not had an antenatal intracranial hemorrhage, 40 percent had severe thrombocytopenia at or before 24 weeks of gestation. Therefore, we recommend that fetal-blood sampling be performed early (at 20 to 24 weeks of gestation) so that the length of the period of severe fetal thrombocytopenia can be minimized by treatment. If even moderate thrombocytopenia is demonstrated by sampling, it appears appropriate to institute treatment, because in untreated fetuses the platelet count will subsequently fall.¹⁷

Treatment of more than 100 cases of fetal alloimmune thrombocytopenia has been described.^{7,9,13,23-28} We have presented data on 73 cases treated by the administration of intravenous immune globulin with or without a glucocorticoid to the mother.¹⁰⁻¹² In these 73 fetuses, the mean platelet count increased by more than 50,000 per cubic millimeter, on the basis of a comparison of the platelet count at the initial cordocentesis with the platelet count at birth or a comparison of the platelet count at birth of the treated fetus with that of an older affected (and untreated) sibling. Treatment very likely prevents intracranial hemorrhage, because no cases were identified in these 73 fetuses.

TABLE 2. RELATION BETWEEN THE PLATELET COUNT OF AN OLDER AFFECTED SIBLING AT BIRTH AND THE INITIAL PLATELET COUNT IN THE STUDY FETUSES.*

	PLATELET COUNT OF OLDER SIBLING AT BIRTH ($\times 10^{-3}/\text{mm}^3$)				
	1-10	11-20	21-30	31-50	>50
No. of fetuses	27	28	19	15	9
Mean platelet count in study fetus ($\times 10^{-3}/\text{mm}^3$)	41 \pm 41	45 \pm 46	30 \pm 26	37 \pm 38	43 \pm 45

*Plus-minus values are means \pm SD.

This study cannot address issues of the natural history of thrombocytopenia beyond the time of initial sampling except in the eight initially untreated fetuses. The frequency of intracranial hemorrhage in fetuses with severe thrombocytopenia also remains unknown, because of the apparent efficacy of antenatal treatment. Data on the incidence and timing of intracranial hemorrhage are only available from series describing the first affected fetuses in families, in which the thrombocytopenia was not diagnosed until after the hemorrhage occurred.^{1,5,6} PI^{A1} typing of all pregnant women would be needed to reduce morbidity and mortality in the first affected fetuses in families.

In summary, thrombocytopenia in fetuses with alloimmune thrombocytopenia as a result of PI^{A1} incompatibility is severe, of early onset, and unremitting. Unfortunately, other than documenting intracranial hemorrhage in an older affected sibling, there is no noninvasive way to identify fetuses at risk. Furthermore, reported treatment results demonstrating the prevention of intracranial hemorrhage have relied on the intensification of therapy in fetuses shown to be unresponsive to initial treatment on the basis of repeated fetal-blood sampling.^{12,20} Therefore, pretreatment and post-treatment fetal-blood samplings are necessary components of antenatal management protocols.

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