Neonatal pearls : safety and efficacy of medication use in fetus and neonate

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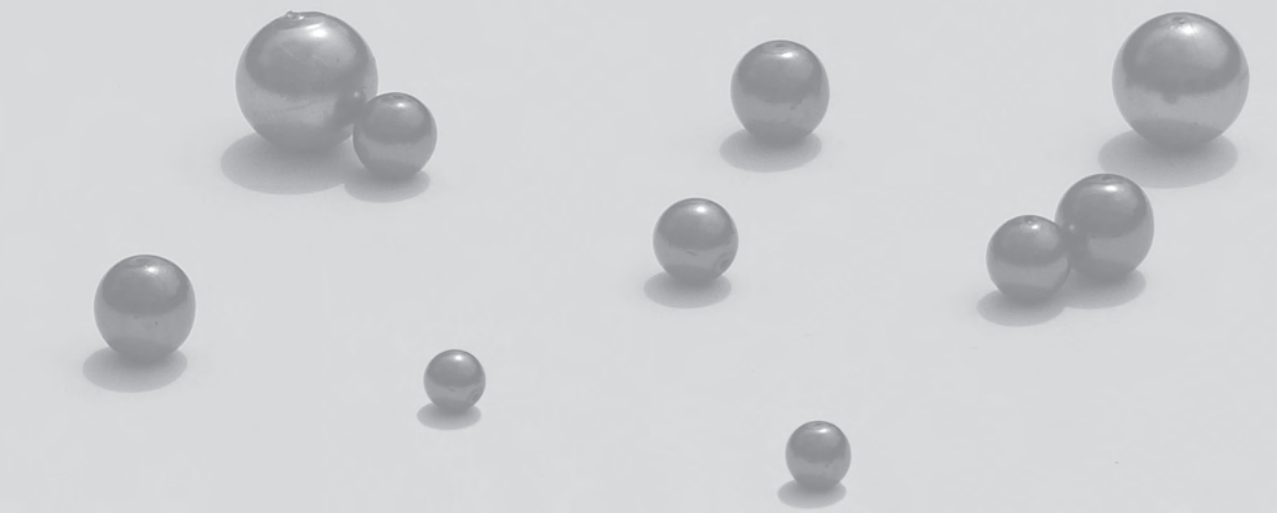
Chapter 6

Outcome and management in neonatal thrombocytopenia due to maternal idiopathic thrombocytopenic purpura



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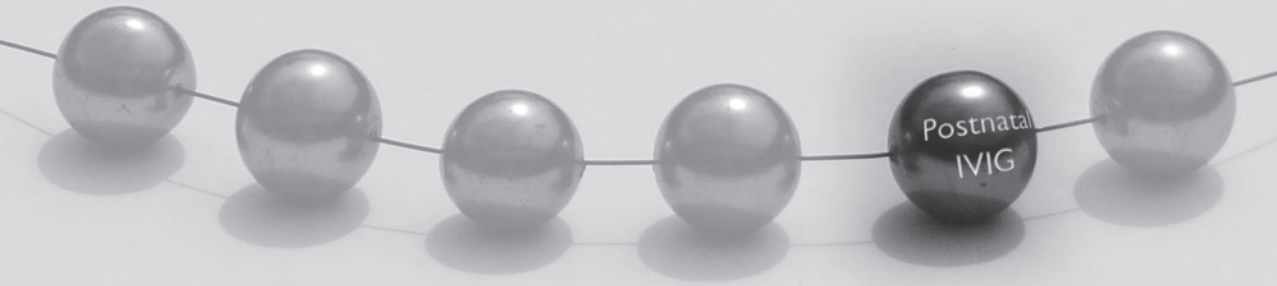

Abstract

Background and objectives

Pregnant women with Idiopathic Thrombocytopenic Purpura (ITP) can deliver neonates with severe thrombocytopenia. Clear evidence declaring the pathophysiological cause of this neonatal thrombocytopenia is lacking, as anti-platelet antibodies are not always detectable in maternal serum. Severe neonatal thrombocytopenia below 50 x 10^9/L is reported in 8-13 % of the neonates from mothers with ITP and, intracranial hemorrhage (ICH) in 0-2.9%. Evidence about the optimal postnatal treatment is scarce. Our objective was to evaluate the outcome and management in neonates with passive ITP.

Materials and methods

All neonates from mothers with ITP born between 1980 and 2011 were included. Platelet counts during the first 10 days, presence of ICH and postnatal treatment were recorded. Maternal characteristics were analysed as possible risk factors for severe neonatal thrombocytopenia.

Results

Sixty-seven neonates were included. Severe thrombocytopenia (<50 x 10^9/L) occurred in 20/67 (29.9%) neonates. In 3 neonates platelet count rose spontaneously, 18 neonates were treated (1 with persistent moderate thrombocytopenia) with: platelet transfusions (3), prednisone (2), IVIG (1), platelet transfusions and IVIG (11), platelet transfusions and prednisone (1). Recurrence of low platelet counts after transfusions were commonly seen. Risk factors for severe neonatal thrombocytopenia were a previous sibling with severe thrombocytopenia and low maternal platelet nadir during pregnancy.

Conclusion

In this cohort severe neonatal thrombocytopenia occurs more frequently than previously reported. To maintain a platelet count above 50 x 10^9/L often multiple transfusions and IVIG are required. Multiple transfusions may be avoided by starting IVIG, when platelet count falls below 50 x 10^9/L after the first platelet transfusion.

Introduction

Idiopathic thrombocytopenic purpura (ITP) has an incidence of 1-10 in 10.000 pregnant women; in one-third ITP presents during pregnancy.[1,2] ITP is considered to be caused by auto-antibodies (IgG) against non-polymorphic platelet antigens, although antibodies cannot be detected in all women with ITP. Hypothetically these IgG antibodies can be transported through the placenta and can cause destruction of fetal platelets, but evidence for this hypothesis lacks.[3,4] Severe thrombocytopenia (<50 x 10^9/L) in infants of mothers with ITP is however present in only 8-13% of the neonates. As opposed to fetal and neonatal allo-immune thrombocytopenia (FNAIT), severe bleeding complications such as intracranial hemorrhage (ICH) are more rare, with a reported incidence of 0-2.9%.[1,2,5-12]

Several risk indicators to predict severe neonatal thrombocytopenia have been explored. Most consistent are a previous sibling with thrombocytopenia[2,6,9,10] and maternal splenectomy for therapy resistant ITP.[1,6,11,13,14] Other factors such as maternal platelet counts (during pregnancy and delivery), presence of detectable anti-platelet antibodies in maternal serum and maternal treatment with corticosteroids and/or intravenous immunoglobulin (IVIG) do not correlate with neonatal platelet count at birth.[1,5,6,8,10,11,13,15] A small randomized controlled trial comparing maternal betamethasone with placebo showed no difference in neonatal platelet count.[16]

The natural course of platelet counts in neonates of mothers with ITP describes a platelet nadir at postnatal day 3-5, after which platelets will stabilize or rise spontaneously.[1,3,12,17,18] However, the optimal postnatal treatment for severe neonatal thrombocytopenia is not evident and includes IVIG, platelet transfusions and/or prednisone. [2,4,6,7,15,19-21] Evidence on the neonatal outcome, risk factors and optimal management is scarce due to lack of studies. The aim of our study is to describe a relative large cohort of neonates, exposed to maternal ITP during pregnancy, with the focus on postnatal management and outcome.

Materials and methods

Study population

Neonates born between April 1980 and October 2011 from mothers with ITP, controlled during pregnancy by the hematology department of the Leiden University Medical Center were included in this study. Criteria for maternal diagnosis of ITP

were isolated thrombocytopenia for which other causes were excluded, normal or hypermegakaryocyte production in bone marrow, normal white and red blood cell counts. Mothers had been treated prior to pregnancy with corticosteroids, intravenous immunoglobuline (IVIG), platelet transfusions, cyclokapron, cyclosporin and/or splenectomy. Maternal autoantibodies were detected by direct platelet Immunofluorescence using anti-IgG and autologous platelets (if above 30 x 10^9/L). Serum antibodies were evaluated by ELISA distinguishing HLA class I antibodies and antibodies against platelet GP IIb/IIIa and Ib/IX. Detection of maternal anti-platelet antibodies against autologous platelets or in serum was not systematically performed as this was not required for diagnosis of ITP, nor to distinguish gestational thrombocytopenia from ITP in mothers presenting with thrombocytopenia in pregnancy.[22]

At birth, platelets were determined from the umbilical cord or capillary as soon as possible on the first day of life; the neonates were examined physically for hematomas and petechiae. Since 1998 cranial ultrasound was routinely made in each neonate with a platelet count of < 50 x 10^9/L. Management protocols changed over time, so different postnatal treatment approaches were followed during the past decades. In most cases indication for platelet transfusion was a platelet count < 50x 10^9/L. Platelet counts were determined at least daily during the first 5 days of life or longer until a spontaneous rise or stable level was observed.

Postnatal neonatal treatment

Platelet transfusions were prepared from bloodgroup O-Rh-D negative donors by apheresis; platelets were leukocyte reduced by filtration prior to storage and volume was reduced prior to transfusion. The administered dose was approximately 20 x 10^9/kg recipient body weight. For newborns with a gestational age below 32 weeks platelets were irradiated (25Gy).

Intravenous immunoglobulin (Immunoglobulin IV/Nanogam, Sanquin, Amsterdam, The Netherlands) was administered in standard dosage of 0.4 g/kg/day. Treatment was continued for 3-5 days, dependent on the severity of neonatal thrombocytopenia and response (i.e. a rising platelet count above 50 x 10^9/L during a couple of successive days).

Prednisone was started with a dosage of 2 mg/kg/day, which was decreased when platelet count increased.

Data collection

Data were collected retrospectively and entered in a database. Antenatal and postnatal baseline characteristics were collected and included maternal diagnosis of ITP before or during pregnancy, maternal splenectomy before pregnancy, maternal medical treatment during pregnancy, nadir of maternal platelet count during pregnancy and last maternal platelet count before delivery, detectable maternal anti-platelet antibodies, mode of delivery, a previous neonate and platelet count of a previous sibling, gestational age and birth weight. Outcome measures were platelet count at birth, presence of hematomas and/or petechiae, occurrence of ICH, need for postnatal treatment, nature of postnatal treatment, duration of thrombocytopenia, interval to reach a platelet count > 50 x 10^9/L and course of platelet counts over time. A subsequent fall or recurrence was defined as a platelet count of > 50 x 10^9/L directly after platelet transfusion, with a subsequent decline below 50 x 10^9/L within 24 hours after the platelet transfusion.

Statistical analysis

Data are reported as median (range), numerical values or categories. Statistical analyses were performed with SPSS Version 18.0 (SPSS Inc., Chicago, IL). As data were not normally distributed, data were analysed with non-parametric test such as Mann-Whitney test (numerical data) and Fisher's Exact test (categorical data). Correlation was analysed using Spearman's correlation. Confounding was prevented using regression analysis. Infants with missing baseline characteristics were excluded from regression analyses.

Results

A total of 83 neonates from 47 mothers with ITP were identified and deemed eligible for our study. Sixteen neonates from 13 mothers were excluded, because of missing data (including platelet counts at birth or platelet counts of the first neonatal days). Sixty-seven neonates of 41 mothers (including 3 twins) were included; for 18 mothers more than 1 pregnancy was analyzed. Seven mothers were excluded for one pregnancy, but included for another pregnancy. Splenectomy was performed before pregnancy in 16 mothers. Maternal anti-platelet antibodies were tested in 38/64 pregnancies and detected in 23 of them (60.5%). ITP was diagnosed prior to pregnancy in 53 pregnancies (82.8%). Antenatal

maternal treatment consisted of IVIG (n=3), prednisone (n=8), cyclokapron (n=2), a combination of prednisone and IVIG (n=4), a combination of IVIG and platelet transfusions (n=2), a combination of IVIG and cyclosporin (n=1) a combination of prednisone, IVIG and splenectomy in the second trimester (n=1). Median nadir of maternal platelet count during pregnancy was 75 x 10^9/L (range 5-347), the last maternal platelet count before delivery was 105 x 10^9/L (range 22-399). Baseline characteristics of the included pregnancies are depicted in table 1. None of the 5 preterm born infants had severe thrombocytopenia. Only one of the neonates born from a mother with ITP diagnosed prior to pregnancy and pre-eclampsia had severe thrombocytopenia. In our study population the incidence of caesarean section was higher compared to the normal Dutch incidence (approximately 15%[23]). The reason for the high caesarean section incidence is not known. The indications for caesarean sections in our study population were not specifically scored; maternal ITP was not per se a contra-indication for vaginal delivery.

Median neonatal platelet count at birth was 202 x 10^9/L (range 4-378). Thirty-four neonates had thrombocytopenia (< 150 x 10^9/L). Severe thrombocytopenia (platelet count < 50 x 10^9/L) was detected in 20 (29.9%) neonates in the first postnatal days, of which 8 (10.6%) had a platelet count of < 20 x 10^9/L. Only 5 neonates had severe thrombocytopenia at birth, whereas the majority developed severe thrombocytopenia within a few days postpartum. Two infants, which developed severe thrombocytopenia in the first 4 days of life, had a platelet count of >150 x 10^9/L at birth. Median age at the time of platelet nadir was 3.0 days (range 1-7) in all neonates.

Routine cranial ultrasound showed no ICH in 14 neonates with severe thrombocytopenia. One neonate showed unilateral (left sided) polymicrogyria on cranial ultrasound and cerebral MRI (magnetic resonance imaging). In 6 neonates cranial ultrasound was not routinely performed, because they were born before 1998, since when the policy of routine cranial ultrasound for neonates with a platelet count below 50 x 10^9/L was introduced. These six neonates showed no clinical neurological signs of intracerebral bleeding. Petechiae were seen in 2 neonates: one had a platelet count of 84 x 10^9/L at birth and a nadir of 54 x 10^9/L on day 7; another had a platelet count of 42 x 10^9/L at birth and 5 x 10^9/L as nadir on day 6.

Table 1. Baseline characteristics of included pregnancies (n=64).

		N = 64
Diagnosis of ITP before pregnancy, n (%)		53 (82.8)
Number of pregnancies a mother, n (%)	1	23 (56.1), 1 twin
	2	14 (34.1), 2 twins
	3	3 (7.3)
	4	1 (2.4)
Maternal age (year)[a]		32.1 (22-40)
Maternal anti-platelet antibodies, n (%)	Tested	38 (59.4)
	Positive	23 (60.5)
Splenectomy before pregnancy, n (%)		16 (25.0)
Maternal treatment during pregnancy, n (%)	No treatment	43 (67.1)
	Prednisone	8 (12.5)
	IVIG	2 (3.1)
	Platelet transfusion	1 (1.6)
	Cyclokapron	2 (3.1)
	Prednisone and IVIG	4 (6.3)
	IVIG and platelet transfusions	2 (3.1)
	Prednisone, IVIG and splenectomy	1 (1.6)
	IVIG and cyclosporin	1 (1.6)
Nadir of platelet count during pregnancy × 10^9/L[a]		75 (5-347)
Last platelet count before delivery × 10^9/L[a]		105 (22-399)
Maternal complications, n (%)	ITP related[b]	3 (4.7)
	Pregnancy complications[c]	7 (10.9)
Cesarean section, n (%)		19 (29.7)
Included infants (including 3 twins)		**N = 67**
Gender (male), n (%)		32 (47.8)
Gestational age (weeks)[a]		39.0 (31-42)
Birth weight (gram)[a]		3240 (1345-4635)

[a] median (range)
[b] Bruising, petechiae, gingival bleeding
[c] Pre-eclampsia, HELLP or hypertension

Table 2. Postnatal outcome and management in 67 neonates born after maternal ITP.

		N = 67
Platelet count at birth x 10^9/L[a]		202 (4-378)
Thrombocytopenia during first week of life, n (%)	101-150 x 10^9/L	34 (50.7)
	51-100 x 10^9/L	25 (37.3)
	21-50 x 10^9/L	20 (29.9)
	< 20 x 10^9/L	8 (11.9)
Platelet nadir x 10^9/L[a]		129 (4-315)
Age at platelet nadir (days)[a]		3 (1-7)
Petechiae, n (%)		2 (3.0)
Postnatal treatment (divided for infants with and without severe thrombocytopenia)		
	> 50 x 10^9/L (n=47)	≤ 50 x 10^9/L (n=20)
No treatment	46 (68.6)	3 (4.5)
IVI		1 (1.5)
Platelet transfusion	1 (1.5)	2 (3.0)
Prednison		2 (3.0)
Platelet transfusion and IVIG		11 (16.4)
Platelet transfusion and prednisone		1 (1.5)

[a] median (range)

Postnatal treatment of infants with severe thrombocytopenia consisted of IVIG (n=1), prednisone (n=2), platelet transfusions (n=2), platelet transfusions combined with IVIG (n=11) and platelet transfusions combined with prednisone (n=1). IVIG was administered during median 5 days (range 3-5). Three children of one mother were treated with prednisone for a period of 11 days to 6 months, exact details of these neonates were not traceable (age of start was unknown in 1 case; exact duration of prednisone therapy given because of prolonged thrombocytopenia was unknown in all 3 cases), due to aged data sources. Three neonates had a quick spontaneous rise in platelet count and did not receive any treatment. Another neonate, without severe thrombocytopenia, but with a persisting platelet count between 50-60 x 10^9/L and petechiae, received 1 platelet transfusion. A general overview of neonatal outcome and management is given in table 2.

Fifteen neonates received median 3 platelet transfusions (range 1-6) per neonate, in 12 neonates combined with IVIG (n=11) or prednisone (n=1). A subsequent fall to a platelet count of <50 x 10^9/L after the platelet transfusion occurred for 9/15 (60.0%) after the first, 8/9 (88.9%) after the second and 6/8 (75.0%) after the third

platelet transfusion. Seven out of 8 infants who had a fall of platelets below 50 x 10^9/L after the first platelet transfusion without IVIG, subsequently received IVIG, and platelets recovered after 2-6 platelet transfusions. IVIG was started at median 3 days (range 1-14) after the first determination of a platelet count < 50 x 10^9/L, median duration until IVIG treatment gained an increasing platelet count above 50 x 10^9/L was 1 day (range 0-8). Table 3 depicts a more detailed overview of the outcome of infants treated with IVIG and/or platelet transfusions.The course of platelet counts of severe thrombocytopenic neonates, receiving treatment for thrombocytopenia, is graphically shown in figure 1.

Table 3. Characteristics of neonates treated with platelet transfusions and/or IVIG

		N = 16
Number of platelet transfusions a neonate[a]		3 (1-6)
Fall of platelet count after platelet transfusion, n (%)[b]	1st	9/15 (60.0)
	2nd	8/9 (88.9)
	3rd	6/8 (75.0)
	4th	5/6 (83.3)
	5th	2/5 (40.0)
	6th	0/3 (0.0)
Increment after first platelet transfusion x 10^9/L [a]		52 (3-147)
Decline of platelet count < 24 hours after platelet transfusion x 10^9/L [a]		66 (15-163)
Interval of start IVIG, after first platelet count < 50 x 10^9/L (days)[a]		3 (1-14)
Duration until platelets count > 50 x 10^9/L and increasing after start IVIG (days)[a]		1 (0-8)

[a] median (range)
[b] Fall of platelet count to < 50 x 10^9/L after platelet transfusion

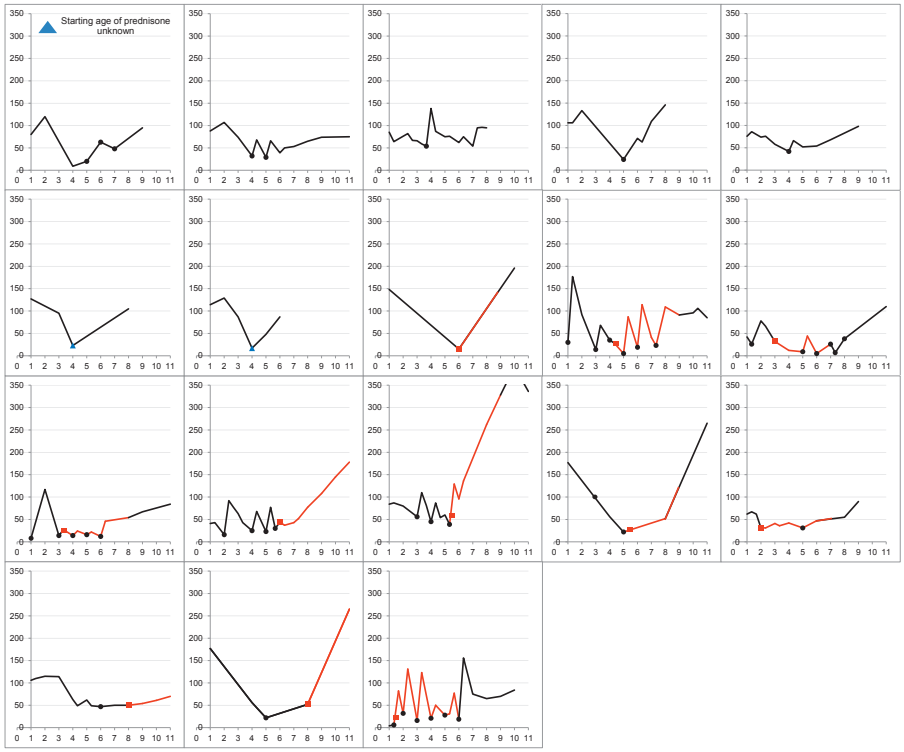

Figure 1. Course of neonatal platelets of all treated neonates per day (n=18).

Legend: Each line indicates one neonate. **Black** dots indicate the timing of platelet transfusions. **Red** squares and line indicate the start and stop of IVIG therapy. **Blue** triangles indicate start of prednisone therapy.

Figure 1 shows that none of the infants receiving treatment for severe thrombocytopenia had a stable and/or rising platelet count above 50 x 10^9/L before the third day of life. Only one of the three neonates with spontaneous rise of platelet counts (without treatment), had this rise already on the second day of life (the other two neonates had their nadir below 50 x 10^9/L on day 6).

Median duration of thrombocytopenia (in all neonates with platelet counts < 150 x 10^9/L) was 11 days (range 3-58). Thirteen of the thirty-four neonates with thrombocytopenia were not followed until a platelet count of >150 x 10^9/L was achieved, but had a stable or rising platelet count between 50-150 x 10^9/L (n=13). In neonates with severe thrombocytopenia platelet counts achieved a safe level above 50 x 10^9/L within median 2.5 days (range 1-17). One neonate received an additional course of IVIG at the age of three weeks, because of a late relapse, with an adequate increment.

Two maternal risk factors for severe neonatal thrombocytopenia were identified, including having an earlier neonate with severe thrombocytopenia (p = 0.032) and a low maternal platelet nadir during pregnancy (p = 0.031). Three mothers had 3 infants and 2 mothers had 2 infants with severe neonatal thrombocytopenia. Platelets at birth and platelet nadir of the first and second sibling were highly correlated (p = 0.001 in Spearman's correlation) in 18 mothers with more than 1 pregnancy (total of 43 neonates), this correlation can be seen in figure 2. We didn't found a relationship between detectable circulating maternal anti-platelet antibodies and severe neonatal thrombocytopenia. An overview of the risk factor analysis can be seen in table 4.

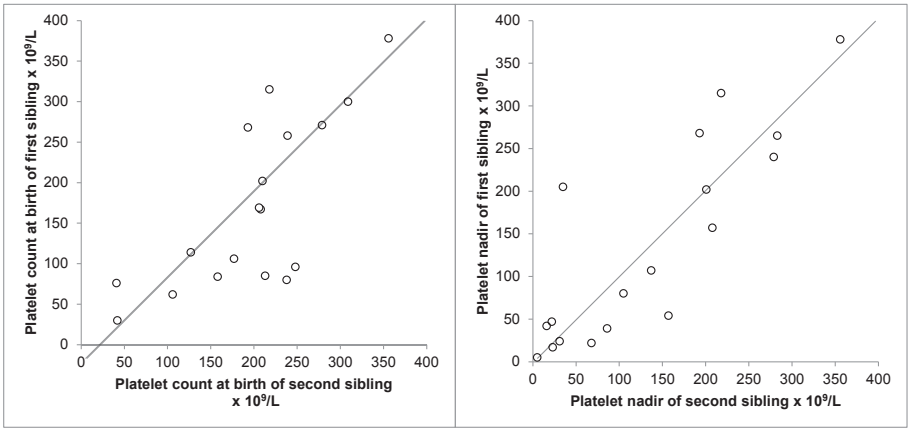

Figure 2. Correlation between platelet counts at birth of the first two siblings of mothers with ITP during pregnancy.

Table 4. Analysis of possible risk factors associated with severe neonatal thrombocytopenia (<50 x 10^9/L).

	Univariate p-value N = 67	Multivariate p-value N = 61
Nadir of maternal platelet count during pregnancy	*0.002*	*0.015*
Last maternal platelet count before delivery	*0.038*	0.084
Splenectomy	0.530	
Diagnosis of ITP before current pregnancy	0.151	
Mode of delivery	0.384	
Detectable maternal anti-platelet antibodies	0.271	
Severe neonatal thrombocytopenia in sibling	*0.003*	*0.016*

Discussion

In this retrospective study the incidence of severe neonatal thrombocytopenia due to maternal ITP is high (29%) with a low incidence of bleeding complications. We report on 20 cases of severe thrombocytopenia, with only 2 cases of symptomatic thrombocytopenia with transient petechiae. A variety of postnatal treatment was used reflecting the lack of international consensus on optimal initial management. The effect of platelet transfusions was often short with frequent recurrence to a low platelet count, requiring additional transfusions and/or IVIG treatment. Our study is one of the larger reporting and analysing the effect of different postnatal treatment strategies. Especially analysing increments after platelet transfusions (currently only recommended for severe bleeding in several guidelines) and reporting individual courses of platelet counts was not performed earlier.[21,24]

Our incidence of severe neonatal thrombocytopenia seems high (29%), but we described all neonates with severe neonatal thrombocytopenia in the first postnatal days, in contrary to the majority of other studies reporting only severe thrombocytopenia at birth.[2,5,7] The incidence of severe thrombocytopenia at birth was only 6% (4/66) in this study, which is comparable with reported incidences by others (8-13%).[2,5-8] The high incidence could also be due to selection bias, because the more complicated cases were more likely to be referred to our tertiary care center (such as mothers with an earlier neonate with severe thrombocytopenia). As platelet counts of excluded neonates were not known, reporting bias caused by their exclusion can not be ruled out. One neonate in our study had severe cerebral injury of antenatal origin (unilateral polymicrogyria). Polymicrogyria is associated with prenatal events including congenital infections, chorioamnionitis, genetic syndromes, metabolic disorders and vascular events. Hypothetically, polymicrogyria in this infant may have resulted after an antenatal ICH due to thrombocytopenia. However, as other causes of polymicrogyria could not be ruled out and bleeding sequels could not be visualized, the occurrence of an antenatal ICH is uncertain. Follow-up at the age of 2 year showed hemiplegia on the right side.[25] In agreement with other studies, we found severe neonatal thrombocytopenia in a sibling a risk factor for severe neonatal thrombocytopenia.[6,9,10] We also observed an association with a low maternal platelet count during pregnancy.[4,7] Evidence about associations between neonatal platelet counts and several maternal factors is conflicting, as most large studies show a lack of association with maternal platelets, antibodies and timing of diagnosis, whereas more severe neonatal thrombocytopenia in mothers which underwent splenectomy was quite frequently described.[1,5,6,9,13]

In the analysis of neonatal course of platelet counts, the effect of postnatal platelet transfusions was frequently short. Only 6/15 infants did not have a subsequent fall after their first platelet transfusion, although 3 of them were already treated with IVIG. Also after the second, third and fourth platelet transfusion recurrence of low platelet counts were common. With a median duration of 1 day (range 0-8) after starting IVIG until an increasing platelet count above 50 x 10^9/L was achieved, these results may indicate that IVIG should be started earlier than was done in this population (median 3 days after the first platelet count of < 50 x 10^9/L), to avoid multiple platelet transfusions. Otherwise, as 3 patients showed spontaneous improvement and 3 patients came to a persistent safe platelet level after one platelet transfusion, IVIG can be withheld in a substantial proportion of infants. Platelet transfusions can be considered in particular for neonates with a very low platelet count at birth, with the expectation that in the majority platelets will further decrease after birth, to tide over the period before IVIG will become effective. Only 3 patients received prednisone, not allowing conclusions to be drawn from our data.

We confirm the greatest risk of neonatal passive ITP to occur postpartum with the lowest platelet count at 3 days after birth. Lacking, apart from the neonatal platelet count of a previous sibling, risk indicators for delivering a severely thrombocytopenic neonate, focus should be turned to postnatal management.[9,11] In this respect this retrospective report is of clinical importance as only two studies could be found that reported on neonates receiving postnatal platelet transfusions, IVIG or prednisone. One study described the effect of postnatal IVIG in 11 neonates, in some cases combined with steroids or platelet transfusions. No significant increments after platelet transfusions as single therapy were reported, but they did not analyze this in detail and individually. IVIG (eventually combined with steroids) had a success rate of 75%.[26] Another study described a series of 6 neonates with disappointing increments after 5 days of IVIG, a subsequent 5 days of prednisone therapy resulted in platelet counts of >150 x 10^9/L in all 6 infants.[27] This study suggested preferring prednisone above IVIG as postnatal therapy, but the adequate platelet increase after 5 days of prednisone could also be a combined effect of IVIG and prednisone. We were the first study analyzing the individual platelet response of neonates with severe thrombocytopenia on platelet transfusions and IVIG.

This study has several limitations, of which the retrospective character is the first one. The sample size was relatively large, compared to other reported populations, however 66 cases is still not a number on which very reliable statistical analyzes are applicable. In regression analysis for multiple variables with such a small sample size, a p-value of

< 0.01 would be more appropriate and preferable. Missing data was another limiting factor, which was caused by the need to collect cases from 30 years ago to have a sample size as large as possible and led to the exclusion of 16 neonates from 13 mothers. All three limitations can create considerable biases, but are the direct consequence of the rarity of the described condition, which makes it really difficult to collect enough cases to apply statistics. With strict cut-off values and definitions we tried to reduce the risk for possible bias as much as possible. Confirmation of our observations in a larger prospective cohorts in future studies is needed trough multicenter international collaboration reporting on all newborns. As it may take weeks before platelet counts are completely recovered, it would be very valuable to look for long term beneficial and adverse effects of different postnatal treatment strategies.

We can conclude that despite severe neonatal thrombocytopenia due to maternal ITP during pregnancy was fairly high in our series, severe bleeding manifestations were rare. As platelet nadir is seen within the first 7 days postpartum, bleeding risks are the highest in the first week, and daily platelet count control is necessary until a stable or rising safe platelet count above 50 x 10^9/L is observed (as advised in guidelines).[20,24,28] In addition should each individual case be evaluated precisely, to determine if daily platelet count measurement is really necessary or once in two days will suffice.

When a platelet transfusion fails to result in a stable increase of platelet counts, further platelet transfusions are not advised without IVIG treatment. Especially, because in a substantial number of neonates it takes some days until IVIG becomes effective, early start is preferable to achieve a safe platelet count of > 50 x 10^9/L more quickly.

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