Thrombocytopenia in Small-for-Gestational-Age Infants

Robert D. Christensen, MD^{a,b,c}, Vickie L. Baer, RN^d, Erick Henry, MPH^e, Gregory L. Snow, PhD^e, Allison Butler, MS^e, Martha C. Sola-Visner, MD^f

abstract

BACKGROUND: Thrombocytopenia is common among small-for-gestational-age (SGA) neonates (birth weight <10th percentile reference range), but several aspects of this thrombocytopenia are unclear, including the incidence, typical nadir, duration, association with preeclampsia, mechanism, and risk of death.

METHODS: Using 9 years of multihospital records, we studied SGA neonates with ≥ 2 platelet counts $<150\,000/\mu\text{L}$ in their first week.

RESULTS: We found first-week thrombocytopenia in 31% (905 of 2891) of SGA neonates versus 10% of non-SGA matched controls ($P < .0001$). Of the 905, 102 had a recognized cause of thrombocytopenia (disseminated intravascular coagulation, early-onset sepsis, or extracorporeal membrane oxygenation). This group had a 65% mortality rate. The remaining 803 did not have an obvious cause for their thrombocytopenia, and we called this “thrombocytopenia of SGA.” They had a mortality rate of 2% ($P < .0001$) and a mean nadir count on day 4 of $93\,000/\mu\text{L}$ (SD $51\,580/\mu\text{L}$, 10th percentile $50\,000/\mu\text{L}$, 90th percentile $175\,000/\mu\text{L}$). By day 14, platelet counts were $\geq 150\,000/\mu\text{L}$ in more than half of the patients. Severely SGA neonates (<1st percentile) had lower counts and longer thrombocytopenia duration ($P < .001$). High nucleated red cell counts at birth correlated with low platelets ($P < .0001$). Platelet transfusions were given to 23%, and counts typically more than tripled. Thrombocytopenia was more associated with SGA status than with the diagnosis of maternal preeclampsia.

CONCLUSIONS: SGA neonates with clearly recognized varieties of thrombocytopenia have a high mortality rate. In contrast, thrombocytopenia of SGA is a hyporegenerative condition of moderate severity and 2 weeks' duration and is associated with evidence of intrauterine hypoxia and a low mortality rate.

Divisions of ^aHematology/Oncology, and ^bNeonatology, Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, Utah; ^cPrimary Children's Hospital, Salt Lake City, Utah; ^dWomen and Newborn's Clinical Program, Intermountain Healthcare, Salt Lake City, Utah; ^eStatistical Data Center, LDS Hospital, Salt Lake City, Utah; and ^fDivision of Neonatal Medicine, Children's Hospital and Harvard Medical School, Boston, Massachusetts

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Address correspondence to Robert D. Christensen, MD, University of Utah Department of Pediatrics, 295 Chipeta Way, Salt Lake City, UT 84108. E-mail: robert.christensen@hsc.utah.edu

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WHAT'S KNOWN ON THIS SUBJECT: Small-for-gestational-age neonates are at risk for thrombocytopenia during the first days and weeks after birth. However, the incidence, duration, severity, responsible mechanism, value of platelet transfusions, and risk of death from this variety of neonatal thrombocytopenia are unknown.

WHAT THIS STUDY ADDS: Ten percent of thrombocytopenic small-for-gestational-age neonates have a recognized cause for low platelets (aneuploidy, extracorporeal membrane oxygenation, disseminated intravascular coagulation); they have a high mortality rate (65%). Ninety percent have a moderate, transient (2 weeks), hyporegenerative thrombocytopenia with a low mortality rate (2%).

Neonates who are born small for gestational age (SGA) (<10th percentile birth weight for a reference population) are at risk for having thrombocytopenia in the first weeks after birth.^{1–6} Some of these neonates have varieties of thrombocytopenia that are readily recognized, such as the consumptive thrombocytopenias accompanying disseminated intravascular coagulation (DIC), extracorporeal membrane oxygenation (ECMO), or early-onset sepsis or the hyporegenerative thrombocytopenias associated with marrow-failure syndromes. Other SGA neonates have a type of thrombocytopenia with no obvious explanation, a variety sometimes termed by exclusion “thrombocytopenia of SGA.”^{1–6} That variety has been the subject of previous reports, but many aspects remain unclear. As a step toward enhancing the knowledge base of the thrombocytopenia of SGA, we conducted an analysis of all SGA infants born in our health care system during a 9-year period. The aims were (1) to identify a group of thrombocytopenic SGA neonates in whom the thrombocytopenia was not a readily apparent variety; and (2) in that group (termed thrombocytopenia of SGA), to identify the incidence, nadir, severity, and duration of the thrombocytopenia and whether it was more closely associated with preeclampsia versus SGA status, assess the responsible mechanisms, and describe the outcomes.

METHODS

Patient Information

Data were collected retrospectively as deidentified limited data sets from archived Intermountain Healthcare records. Intermountain Healthcare is a not-for-profit healthcare system that owns and operates 19 hospitals with labor and delivery units in Utah and Idaho. The information collected was limited to the information in this

report. Patient records were accessed if the neonate had a date of birth from January 1, 2004, to December 31, 2013. The Intermountain Healthcare Institutional Review Board approved this as a deidentified data-only study as not requiring the consent of individual subjects.

Blood Cell Counts and Platelet Transfusions

Platelet counts and mean platelet volumes (MPVs) were determined in all hospitals with the Beckman Coulter LH750 Hematology Analyzer (Fullerton, CA) from 2004 to mid-2012. After mid-2012, platelet counts and MPVs were determined by using Sysmex counters (Sysmex America, Lincolnshire, IL). All blood tests were performed in accordance with Intermountain Healthcare Laboratory Services standard operating procedures. Nucleated red blood cells were quantified using either automated cell counts, performed in accordance with the hematology analyzer manufacturer's instructions, or manual enumeration, performed by certified medical technologists on Wright-stained blood smears, counting a minimum of 100 nucleated cells per test. The reference intervals for complete blood count parameters are those we previously published from Intermountain Healthcare databases.⁷

Guidelines for administering platelet transfusions in the Intermountain Healthcare NICUs during this period have been published.^{8,9} All platelet transfusions were type specific or AB (Rh positive or negative) and were derived from apheresis. They were not pooled or volume-reduced, but all were subjected to leukofiltration and irradiation and administered in a volume of 10 to 15 mL/kg body weight. Gestational age was determined by obstetrical assignment unless changed by the neonatologist on the basis of gestational age assessment (physical examination and neurologic-neurodevelopmental findings).

Neonates were classified as SGA if their weight at birth was <10th percentile for gestational age, using normative values from our Intermountain Healthcare population.¹⁰ Severity of SGA was classified according to 3 categories: <1st percentile (severe), first to fifth percentile (moderate), and sixth to 10th percentile (mild). Preeclampsia was identified from case-mix records using the following definitions from the *International Classification of Diseases, Ninth Revision, Clinical Modification* (Ingenix Expert, Eden Prairie, MN): 6425, 6426, and 6427.

SGA neonates were matched 1:1 with neonates from the same hospitals born during the same period of time who were not SGA. Matching was performed on the basis of gestational age (within 1 week) and year/month of birth (within 1 month). Early thrombocytopenia was defined as ≥ 2 platelet counts $<150\,000/\mu\text{L}$ during the first week after birth. Using chart reviews and electronic reviews of laboratory data, patients whose data would otherwise qualify for inclusion in the SGA and thrombocytopenia group were excluded if they were recognized to have another variety of thrombocytopenia. These specifically included early-onset sepsis, congenital cytomegalovirus (CMV) or other congenital viral infection, ECMO treatment, immune-mediated thrombocytopenia, aneuploidy, varieties of severe congenital thrombocytopenia, or DIC. DIC was diagnosed by the combination of hypofibrinogenemia for age,¹¹ schistocytosis,¹² prolongation of prothrombin time and activated partial thromboplastin time for age,¹¹ and elevated D-dimers.

Data Collection and Statistical Analysis

The program used for data collection was a modified subsystem of Clinical Workstation. The 3M Company (Minneapolis, MN) approved the structure and definitions of all data points for use within the program.

Data were managed and accessed by authorized data analysts. Means and standard deviations were used to express values in groups that were normally distributed, and medians and ranges to express values in groups that were not. Differences in categorical variables were assessed by using the Fisher exact test or χ^2 . Student nonpaired *t* test was used to assess continuous variables. Statistical analysis used the R Foundation package (Statistical Computing, Vienna Austria). The mixed-effects model used NIME software, version 3.1-105, also from the R package. Statistical significance was set as $P < .05$.

RESULTS

Incidence, Severity, and Duration of Thrombocytopenia

During the 9-year period studied, 24 036 neonates were admitted to an

Intermountain Healthcare NICU, and 3964 of these were SGA (Fig 1). Of the SGA infants, 2891 had ≥ 2 platelet counts measured in the first week, and 905 (31.5%) of these had ≥ 2 platelet counts $< 150\,000/\mu\text{L}$, thereby qualifying for the definition of early (first-week) thrombocytopenia. Thus the incidence of thrombocytopenia in our SGA neonates was 31.5%, which was higher than the 10.0% incidence of early thrombocytopenia among 2891 non-SGA control neonates matched for gestational age ($P < .0001$) (Fig 1). The 2891 non-SGA controls were well matched with the 2891 SGA neonates on the basis of gestational age (Table 1), but (as expected) the non-SGA control group had a higher birth weight; lower rates of cesarean delivery, maternal eclampsia or preeclampsia, and mortality; and proportionately more males compared with the SGA neonates.

Of the 905 thrombocytopenic SGA neonates, 102 had a condition (besides SGA) that might have caused their thrombocytopenia (Fig 1). These conditions included treatment with ECMO ($n = 28$), aneuploidy ($n = 30$, 3 of whom were also on ECMO), early-onset culture-positive bacterial sepsis ($n = 6$), congenital CMV ($n = 6$), congenital marrow failure syndromes ($n = 4$), alloimmune thrombocytopenia ($n = 2$), DIC ($n = 8$), and various malformation syndromes ($n = 18$). These 102 neonates were excluded from further analysis, leaving 803 with a condition we termed thrombocytopenia of SGA (Table 2).

Platelet counts in these 803 are shown in Fig 2. The reference interval for platelet counts of neonates during their first 3 weeks (5th to 95th percentile limits), which we published previously,¹³ is shown by the shaded area for comparison. The lowest platelet counts were typically on day 4, with a mean nadir of $93\,000/\mu\text{L}$ (SD $51\,580/\mu\text{L}$, 10th percentile $50\,000/\mu\text{L}$, 90th percentile $175\,000/\mu\text{L}$). By day 14 of life, the platelet count had increased to $\geq 150\,000/\mu\text{L}$ in half of the infants and was $\geq 100\,000/\mu\text{L}$ in 70%. By day 21, the count was $\geq 150\,000/\mu\text{L}$ in about two-thirds (Fig 2). The most severely SGA neonates (birth weight $< 1\text{st}$ percentile reference range) had lower platelet counts than those with moderate ($P = .013$) or mild ($P = .005$) SGA (Fig 3). The severe SGA group also had a longer duration of thrombocytopenia, with 50% having platelet counts $< 150\,000/\mu\text{L}$ by 28 to 30 days.

SGA and Preeclampsia

Associations of thrombocytopenia with SGA status versus maternal preeclampsia were sought by comparing the lowest platelet count during the first 4 days of life among 4 groups of NICU patients matched for gestational age (within 1 week) (Fig 4). Neonates who were SGA but no maternal preeclampsia was

FIGURE 1

Study flow diagram to identify neonates with thrombocytopenia of SGA.

TABLE 1 SGA Neonates and Non SGA Matched Controls Admitted to a NICU

Group	<i>n</i>	Gestational Age, wks	Birth Weight, g	Male Gender	Cesarean Delivery	Eclampsia or Preeclampsia	Mortality ^a
SGA	2891	35 ± 3	2044 ± 634	49.8	53.9	12.8	4.1
Not SGA	2891	35 ± 3	2841 ± 816	59.8	44.4	1.6	1.6
<i>P</i>		.999	<.0001	<.0001	<.0001	<.0001	<.0001

SGA neonates (*n* = 2891) admitted to a NICU who had at least 2 platelet counts obtained in the first week were matched by gestational age and date of birth (within 1 month) with non-SGA neonates admitted to a NICU with at least 2 platelet counts in the first week, to assess any association between SGA status and early (first-week) thrombocytopenia.

Values are expressed as mean ± SD or %.

^a Deaths in the NICU.

diagnosed (Group 1) had lower platelet counts (mean 153 000/ μ L) than did those born to women with preeclampsia but were not SGA (Group 2) (197 000/ μ L, *P* < .0001, 95% confidence interval on the difference 22 to 64). Using linear regression to account for gestational and birth weight, the point estimate of the difference in the 2 groups was still significant (*P* = .0189, 95% confidence interval on the difference 10 to 61). Among SGA neonates, the presence or absence of preeclampsia made no difference in the platelet count. Thus, preeclampsia may not be associated with a risk of neonatal thrombocytopenia over and above the risk associated with SGA status.

Nucleated Red Blood Cell Count, MPV, and Response to Platelet Transfusion

Among the 803 neonates we labeled as having thrombocytopenia of SGA,

an elevated nucleated red blood cell count (NRBC, per microliter) at birth correlated with a low platelet count in the first week after birth (Fig 5) (*P* < .01). MPV measurements accompanying the platelet counts of the 803 thrombocytopenic neonates over their first week after birth are displayed in Fig 6. Overlying the values in the shaded area is the MPV reference interval (5th to 95th percentile limits) that we published previously.¹³

Of the 803 neonates with thrombocytopenia of SGA, 182 (23%) received 1 to 33 apheresis platelet transfusions. Reviews indicated that 98% of the transfusions were given prophylactically, meaning the patient did not have active bleeding. Platelet counts before the transfusions ranged from 6000 to 110 000/ μ L; median count was 49 000/ μ L. The rise in

platelet count after transfusion, calculated by subtracting the pretransfusion count from the count performed 1 to 24 hours after transfusion, was 118 990 ± 59 736/ μ L. Figure 7 shows the increase and subsequent decrease in platelet counts after platelet transfusion. For ease of comparison, all platelet counts were normalized to percentage of the pretransfusion platelet count.

Outcomes

Ten SGA neonates had severe thrombocytopenia (<50 000/ μ L) that persisted for at least 4 weeks (Table 2). Nine of the 10 were severely SGA (<1st percentile at birth). Four of these had no apparent explanation, other than the SGA status, for persistent severe thrombocytopenia. The other 6 had developed late-onset

TABLE 2 Ten SGA Neonates Classified as Having Severe and Persistent Thrombocytopenia of SGA

Birth Weight, g	SGA Percentile	Gestational age at birth, wk/d	Maternal Preeclampsia, Eclampsia, or HELLP	Lowest platelet count in the first 2 wks after birth, / μ L	Lowest platelet count at 4–6 weeks, / μ L	Platelet Transfusions Received, <i>n</i>	Diagnosis at 4–6 wks	Outcome
350	<1st	24/0	None	27 000	48 000	21	Necrotizing enterocolitis with bowel resection ^a	Died at 6 mo in NICU
406	<1st	22/6	HELLP	42 000	30 000	33		Died at home at 7 mo
420	<1st	24/5	HELLP	52 000	23 000	31	<i>Candida</i> sepsis ^a	Died at home at 17 mo
470	<1st	26/5	Eclampsia	46 000	40 000	8		Lived
480	<1st	23/6	Preeclampsia	49 000	38 000	11		Lived
510	<1st	26/4	Preeclampsia	36 000	36 000	8	<i>Klebsiella</i> sepsis	Lived
565	<1st	27/0	HELLP	121 000	47 000	10	Necrotizing enterocolitis with bowel perforation and resection	Lived
580	<1st	27/1	None	52 000	10 000	16	Necrotizing enterocolitis with <i>Enterobacter cloacae</i> sepsis ^a	Lived
663	<1st	29/2	None	36 000	37 000	4		Lived
2100	10th	35/1	None	73 000	12 000	8	Complex congenital heart disease, <i>Klebsiella</i> sepsis	Died in hospice at 5 y

Ten SGA neonates who were classified as having thrombocytopenia of SGA and, when tabulated 28 to 42 days after birth, were still severely thrombocytopenic (<50 000/ μ L) and receiving platelet transfusions. Six of the 10 had "late consumptive thrombocytopenia" and 4 had no explanation for persistent thrombocytopenia, other than thrombocytopenia of SGA.

^a No explanation, other than severe SGA, for severe thrombocytopenia continuing at 4 to 6 wks.

FIGURE 2
Platelet counts of 803 neonates with thrombocytopenia of SGA during their first 30 days. Median platelet count, first and third interquartile range (box), and 10th and 90th percentile values (whiskers) are shown. The shaded area shows the normal reference interval for platelet counts of neonates of ≥ 35 weeks' gestation (modified from Wiedmeier et al¹³). Also shown are platelet counts of 10 of the 803 whose thrombocytopenia persisted when checked in the 28- to 42-day window. Four of the 10 (open circles, solid line) had no explanation for prolonged thrombocytopenia besides thrombocytopenia of SGA, and 6 (closed circles, dashed line) had developed either necrotizing enterocolitis or late-onset sepsis (see Table 2 for details of these 10).

thrombocytopenia accompanying necrotizing enterocolitis or sepsis. Using data from the first days after birth, focusing on birth weight,

gestational age, or platelet counts in the first 4 days, we were not able to recognize these 6 as distinct from the other 2885 in the group of 2891.

FIGURE 3
Platelet counts measured on day 4 of life (the mean nadir of platelet count) of SGA neonates according to birth weight percentile. Counts are grouped from neonates weighing less than first percentile, first to fifth percentile, sixth to 10th percentile, and 11th to 99th percentile for gestational age (the latter group considered controls). In each of the weight categories, the median platelet count is shown along with the first and third interquartile range (box) and the 10th and 90th percentile values (whiskers).

Mean platelet counts of these 10 during their first 3 weeks (grouped as the 4 with no explanation for prolonged thrombocytopenia and the 6 with NEC or late-onset sepsis) are shown in Fig 2 along with the entire group of 803 with thrombocytopenia of SGA (box and whiskers) and the normal controls (shaded area). This group of 10 with persistent severe thrombocytopenia received 4 to 33 platelet transfusions. All of these were prophylactic, for platelet counts $< 50\,000$ to $60\,000/\mu\text{L}$, with no signs of bleeding.

Of the 1986 SGA neonates in whom thrombocytopenia was not identified, 34 (2%) died. In contrast, of the 905 SGA neonates in whom thrombocytopenia was identified, 85 (9%) died ($P < .0001$) (data shown in Supplementary Table 3). Of the 102 SGA neonates with known varieties of thrombocytopenia (eg, ECMO or DIC), 66 (65%) died. However, of the 803 SGA neonates with thrombocytopenia of SGA, 19 (2%) died ($P < .0001$ vs. SGA neonates with known varieties of thrombocytopenia). All thrombocytopenic SGA neonates with DIC who died had bleeding problems at the time of death, predominantly pulmonary hemorrhage. None of those with trisomy 18 or 13 who died had bleeding problems (shown in Supplementary Table 3).

Logistic regression was performed to identify clinical variables predictive of severe ($< 50\,000/\mu\text{L}$) and prolonged (≥ 2 weeks) thrombocytopenia, which we judged could be relevant to future testing of thrombopoietin receptor agonists such as romiplostim.¹⁴ This medication takes 7 to 10 days to elevate the platelet count; therefore, neonates recognized within the first days as being very likely to remain severely thrombocytopenic for ≥ 2 weeks might be candidates for experimental treatment. Three variables had predictive correlations: (1) gestational age at birth (shorter gestation was associated with higher likelihood of severe, persistent

FIGURE 4

Platelet counts during the first 4 days after birth among 4 groups of NICU admissions (each $n = 100$): (1) SGA but no preeclampsia, (2) preeclampsia but not SGA, (3) both SGA and preeclampsia, and (4) neither SGA nor preeclampsia.

thrombocytopenia); (2) gender (males were more likely to have severe, persistent thrombocytopenia); and (3) lowest platelet count in the first week (generally on day 4). However, the models were insufficiently predictive for individual patients, and no variable had an odds ratio >1.45

predicting severe and prolonged thrombocytopenia.

DISCUSSION

Thrombocytopenia is a common problem among patients in NICUs.^{1,2,5,6,14–18} The majority have acquired varieties of consumptive

thrombocytopenia accompanying bacterial or fungal sepsis or necrotizing enterocolitis.^{1,2,5,6} Rare varieties of hyporegenerative thrombocytopenia accompany aneuploidy or syndromes involving thrombopoietic failure.^{1–3} A separate variety of early thrombocytopenia has been described among neonates who are SGA. The first report of this entity was by Meberg et al from Oslo in 1977.¹⁹ They studied 23 neonates weighing <10 th percentile who, with no other explanation, had ≥ 1 platelet count $<100\,000/\mu\text{L}$ in the first days after birth. The platelet counts generally increased to $>150\,000/\mu\text{L}$ by day 15 of life, and none had pathologic bleeding. The authors speculated that this thrombocytopenia was the result of chronic hypoxia in utero induced by placental insufficiency. In 1983, Shuper et al from Israel reported 14 SGA infants with ≥ 1 platelet counts $<100\,000/\mu\text{L}$ and no other explanation for the thrombocytopenia.²⁰ Elevated NRBCs at birth were common in the thrombocytopenic neonates; thus they postulated, as had Meberg et al, that the condition was due to reduced platelet production associated with chronic intrauterine hypoxia. Our present study used a large multihospital dataset to better define this condition, which has come to be termed thrombocytopenia of SGA^{1–6}.

We began by identifying all patients in the last 9 years admitted to an Intermountain Healthcare NICU with a birth weight <10 th percentile.¹⁰ We then determined how many of these SGA neonates had ≥ 2 platelet counts drawn during their first week, and how many of those had ≥ 2 platelet counts $<150\,000/\mu\text{L}$. A low platelet count in a neonate can be real or artifactual; the latter typically involves platelet clumping, either on the wound when blood is drawn slowly from a capillary puncture or within the specimen tube.²¹ We aimed to reduce the contamination of our dataset with artifactual thrombocytopenia by requiring 2 low counts.

FIGURE 5

Among 803 neonates with thrombocytopenia of SGA, NRBC (per microliter) at birth is compared with lowest platelet count recorded in the first 3 days after birth.

FIGURE 6 MPV (femtoliters). Values are shown from 803 neonates who met a definition of thrombocytopenia of SGA. Median values, first and third interquartile range (box), and 10th and 90th percentile values (whiskers) are shown. The shaded area represents the normal reference interval for MPV (modified from Wiedmeier et al¹³).

After identifying all SGA neonates who had early (first-week) thrombocytopenia, we sought to cull those associated with a recognized cause of thrombocytopenia. This was done so that we could tentatively classify the others as having the exclusionary diagnosis of

thrombocytopenia of SGA. We found that ~10% of thrombocytopenic SGA neonates had a readily identifiable variety of thrombocytopenia, and that group had a high mortality rate (65%). In contrast, 90% had a low-mortality variety with the following characteristics. (1) The

FIGURE 7 Platelet counts after apheresis platelet transfusions to 196 neonates. All values are normalized to percentage of the pretransfusion platelet count (all pretransfusion counts are shown as 100%). Median values, first and third interquartile range (box), and 10th and 90th percentile values (whiskers) are shown. The peak and characteristics of the subsequent decrease are used to infer the kinetic mechanism responsible for the thrombocytopenia (reduced platelet production versus accelerated platelet destruction).

thrombocytopenia appears to be primarily hyporegenerative as opposed to accelerated platelet consumption or destruction. We made this judgment on the basis of normal MPVs and good responses to platelet transfusions. (2) The low platelet counts are associated with intrauterine hypoxemia (elevated NRBC) and with the pathology that creates fetal growth restriction, not the pathology that produces preeclampsia without fetal growth restriction. (3) The thrombocytopenia is typically only moderately severe (mean nadir count of 93 000/ μ L) with a typical nadir on about day 4 and a typical duration (days to a count >150 000/ μ L) of 2 weeks. However, those with severe SGA tend to have lower counts and a longer duration.

Cremer et al also suggested that thrombocytopenia of SGA is the kinetic result of reduced platelet production, by measuring the immature platelet fraction.²² They found a trend toward lower immature fractions (suggesting reduced platelet production) in thrombocytopenic SGA neonates compared with thrombocytopenic neonates who had infection, in whom the mechanism is likely accelerated platelet utilization.

Reduced platelet production was also the mechanism suggested by the work of Murray et al, who observed that preterm infants with thrombocytopenia had fewer circulating megakaryocyte progenitors than nonthrombocytopenic controls.²³ Likewise, we reported few megakaryocytes in the marrow of 3 thrombocytopenic SGA neonates.²⁴ Both Murray et al²³ and Sola et al²⁴ reported low plasma thrombopoietin concentrations, suggesting inadequate upregulation of thrombopoietin production. The hypothesis that the thrombocytopenia of SGA is primarily due to thrombopoietin deficiency

in utero is consistent with these studies but remains to be confirmed.

The molecular mechanisms resulting in thrombocytopenia of SGA may be similar to that causing thrombocytopenia of perinatal asphyxia.²⁵ We suspect that fetal hypoxia is causally involved in both varieties, which is consistent with the study of McDonald et al,²⁶ in adult mice subjected to hypoxia, and the marrow culture studies of Saxonhouse et al.^{27,28}

If the thrombocytopenia of SGA is determined to be the result of thrombopoietin deficiency, it will remain unclear whether thrombopoietin receptor agonists such as romiplostim or eltrombopag will be of value in treating this condition.^{14,29} Most neonates with the thrombocytopenia of SGA are not severely thrombocytopenic; thus perhaps no treatment is warranted for most. Moreover, romiplostim and eltrombopag require 7 to 10 days between commencement of dosing and a significant increase in platelet count, and half of the neonates with this variety of thrombocytopenia have platelet counts $>150\,000/\mu\text{L}$ by day 14. Because a subset of patients remain severely thrombocytopenic for >14 days, and some for >28 days, the efficacy, risks, and benefits of administering thrombopoietin agonists to that group might warrant future study, if they could be identified in the first week. We found that these are typically males born at very early gestational age with very low counts initially. However, we were unable to accurately predict during the first week which infants would still have severe, persistent thrombocytopenia after 2 weeks.

One treatment option for neonates with thrombocytopenia of SGA is platelet transfusion, but as

highlighted by Josephson et al, platelet transfusion strategies for neonates lack a strong evidence base.³⁰ There is substantial disagreement on neonatal platelet transfusion thresholds, but it is widely accepted that platelet transfusions should be given to neonates if their platelet count falls below $20\,000/\mu\text{L}$.^{1,31,32} Counts that low should be rare in neonates with thrombocytopenia of SGA. From our present data, 90% of platelet count among neonates with this diagnosis will be $>50\,000/\mu\text{L}$; thus perhaps 10% will be $<50\,000/\mu\text{L}$. In our present analysis, 182 of the 803 neonates with thrombocytopenia of SGA received platelet transfusions. In retrospect, we question how many of those were beneficial. Very few had a platelet count $<20\,000/\mu\text{L}$, most had a pretransfusion platelet count $>50\,000/\mu\text{L}$, and almost all were transfused prophylactically with no bleeding problems prompting the transfusion.

We recognize several significant problems in our retrospective analysis. For instance, surely some relevant data were sometimes missing from the charts or electronic databases, and bias may have been unintentionally introduced. Also, platelet counts after platelet transfusions were not obtained on a standard schedule, and platelet transfusions were given to some and not to others without any clear explanation. Also, changes in obstetrical and neonatology practices occurred during the 9 years of study. The practice changes we recognize are the overall reduction in NICU transfusions during this period⁸ and the specific reduction in platelet transfusions on the basis of a change from platelet count–based guidelines to platelet mass–based guidelines.⁹ In

addition, in our studies of associations with preeclampsia, we captured only those women coded as having HELLP (syndrome of hemolysis, elevated liver enzymes, and low platelets), eclampsia, or severe or moderately severe preeclampsia, not those with mild or unspecified preeclampsia; thus we might have ignored associations between thrombocytopenia and mild preeclampsia. Last, we did not identify the molecular mechanisms involved in the association between SGA status and thrombocytopenia. Clarifying this mechanism should be the topic of future investigations, as it might suggest novel preventive or treatment approaches.

Considering the weaknesses and strengths of our data, we maintain it is reasonable to conclude that about one-third of SGA infants have early thrombocytopenia. About 10% of these have an obvious cause of thrombocytopenia such as sepsis, aneuploidy, or ECMO treatment, and this group has a high mortality rate (65% in our dataset). However, 90% of thrombocytopenic SGA neonates have a different variety that could be termed thrombocytopenia of SGA. Those neonates should have a low mortality rate, yet some will probably receive multiple platelet transfusions.

ABBREVIATIONS

CMV: cytomegalovirus
DIC: disseminated intravascular coagulation
ECMO: extracorporeal membrane oxygenation
MPV: mean platelet volume
NRBC: nucleated red blood cell count
SGA: small for gestational age

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REFERENCES

- Carr R, Kelly AM, Williamson LM. Neonatal thrombocytopenia and platelet transfusion: a UK perspective. *Neonatology*. 2015;107(1):1–7
- Sola-Visner MC, Saxonhouse MA. Acquired thrombocytopenia. In: deAlarcon PA, Werner EJ, Christensen RD, eds. *Neonatal Hematology*, 2nd ed. Cambridge, UK: Cambridge University Press; 2013:162–164
- Wasiluk A, Mantur M, Kemona H, Szczepański M, Jasińska E, Milewski R. Thrombopoiesis in small for gestational age newborns. *Platelets*. 2009;20(7):520–524
- Beiner ME, Simchen MJ, Sivan E, Chetrit A, Kuint J, Schiff E. Risk factors for neonatal thrombocytopenia in preterm infants. *Am J Perinatol*. 2003;20(1):49–54
- Baer VL, Lambert DK, Henry E, Christensen RD. Severe Thrombocytopenia in the NICU. *Pediatrics*. 2009;124(6). Available at: www.pediatrics.org/cgi/content/full/124/6/e1095
- Stanworth SJ, Clarke P, Watts T, et al; Platelets and Neonatal Transfusion Study Group. Prospective, observational study of outcomes in neonates with severe thrombocytopenia. *Pediatrics*. 2009;124(5). Available at: www.pediatrics.org/cgi/content/full/124/5/e826
- Christensen RD, Henry E, Jopling J, Wiedmeier SE. The CBC: reference ranges for neonates. *Semin Perinatol*. 2009;33(1):3–11
- Gerday E, Baer VL, Lambert DK, et al. Testing platelet mass versus platelet count to guide platelet transfusions in the neonatal intensive care unit. *Transfusion*. 2009;49(10):2034–2039
- Baer VL, Henry E, Lambert DK, et al. Implementing a program to improve compliance with neonatal intensive care unit transfusion guidelines was accompanied by a reduction in transfusion rate: a pre-post analysis within a multihospital health care system. *Transfusion*. 2011;51(2):264–269
- Christensen RD, Henry E, Kiehn TI, Street JL. Pattern of daily weights among low birth weight neonates in the neonatal intensive care unit: data from a multihospital health-care system. *J Perinatol*. 2006;26(1):37–43
- Christensen RD, Baer VL, Lambert DK, Henry E, Ilstrup SJ, Bennett ST. Reference intervals for common coagulation tests of preterm infants (CME). *Transfusion*. 2014;54(3):627–632, quiz 626
- Christensen RD, Yaish HM, Lemons RS. Neonatal hemolytic jaundice: morphologic features of erythrocytes that will help you diagnose the underlying condition. *Neonatology*. 2014;105(4):243–249
- Wiedmeier SE, Henry E, Sola-Visner MC, Christensen RD. Platelet reference ranges for neonates, defined using data from over 47,000 patients in a multihospital healthcare system. *J Perinatol*. 2009;29(2):130–136
- Sallmon H, Gutti RK, Ferrer-Marín F, Liu ZJ, Sola-Visner MC. Increasing platelets without transfusion: is it time to introduce novel thrombopoietic agents in neonatal care? *J Perinatol*. 2010;30(12):765–769
- Kahn DJ, Richardson DK, Billett HH. Inter-NICU variation in rates and management of thrombocytopenia among very low birth-weight infants. *J Perinatol*. 2003;23(4):312–316
- Muthukumar P, Venkatesh V, Curley A, et al; Platelets Neonatal Transfusion Study Group. Severe thrombocytopenia and patterns of bleeding in neonates: results from a prospective observational study and implications for use of platelet transfusions. *Transfus Med*. 2012;22(5):338–343
- Ferrer-Marín F, Stanworth S, Josephson C, Sola-Visner M. Distinct differences in platelet production and function between neonates and adults: implications for platelet transfusion practice. *Transfusion*. 2013;53(11):2814–2821, quiz 2813
- McPherson RJ, Juul S. Patterns of thrombocytosis and thrombocytopenia in hospitalized neonates. *J Perinatol*. 2005;25(3):166–172
- Meberg A, Halvorsen S, Orstavik I. Transitory thrombocytopenia in small-for-date infants, possibly related to maternal smoking. *Lancet*. 1977;2(8032):303–304
- Shuper A, Mimouni F, Merlob P, Zaizov R, Reisner SH. Thrombocytopenia in small-for-gestational-age infants. *Acta Paediatr Scand*. 1983;72(1):139–140
- Christensen RD, Sola MC, Rimsza LM, McMahan MJ, Calhoun DA. Pseudothrombocytopenia in a preterm neonate. *Pediatrics*. 2004;114(1). Available at: www.pediatrics.org/cgi/content/full/114/1/e273
- Cremer M, Weimann A, Schmalisch G, Hammer H, Bühner C, Dame C. Immature platelet values indicate impaired megakaryopoietic activity in neonatal early-onset thrombocytopenia. *Thromb Haemost*. 2010;103(5):1016–1021
- Murray NA, Watts TL, Roberts IA. Endogenous thrombopoietin levels and effect of recombinant human thrombopoietin on megakaryocyte precursors in term and preterm babies. *Pediatr Res*. 1998;43(1):148–151
- Sola MC, Calhoun DA, Hutson AD, Christensen RD. Plasma thrombopoietin concentrations in thrombocytopenic and non-thrombocytopenic patients in a neonatal intensive care unit. *Br J Haematol*. 1999;104(1):90–92
- Christensen RD, Baer VL, Yaish HM. Thrombocytopenia in late preterm and term neonates after perinatal asphyxia. *Transfusion*. 2015;55(1):187–196
- McDonald TP, Cottrell MB, Clift RE, Jackson CW. Effects of hypoxia on megakaryocyte size and number of C3H and BALB/c mice. *Proc Soc Exp Biol Med*. 1992;199(3):287–290
- Saxonhouse MA, Rimsza LM, Christensen RD, et al. Effects of anoxia on megakaryocyte progenitors derived from cord blood CD34pos cells. *Eur J Haematol*. 2003;71(5):359–365
- Saxonhouse MA, Rimsza LM, Stevens G, Jouei N, Christensen RD, Sola MC. Effects of hypoxia on megakaryocyte progenitors obtained from the umbilical cord blood of term and preterm

- neonates. *Biol Neonate*. 2006;89(2): 104–108
29. Sola-Visner M. Platelets in the neonatal period: developmental differences in platelet production, function, and hemostasis and the potential impact of therapies. *Hematol Am Soc Hematol Educ Program* 2012;2012:506–511
 30. Josephson CD, Glynn SA, Kleinman SH, Blajchman MA; State-of-the Science Symposium Transfusion Medicine Committee. A multidisciplinary “think tank”: the top 10 clinical trial opportunities in transfusion medicine from the National Heart, Lung, and Blood Institute-sponsored 2009 state-of-the-science symposium. *Transfusion*. 2011;51(4): 828–841
 31. Cremer M, Sola-Visner M, Roll S, et al. Platelet transfusions in neonates: practices in the United States vary significantly from those in Austria, Germany, and Switzerland. *Transfusion*. 2011;51(12):2634–2641
 32. Josephson CD, Su LL, Christensen RD, et al. Platelet transfusion practices among neonatologists in the United States and Canada: results of a survey. *Pediatrics*. 2009;123(1). Available at: www.pediatrics.org/cgi/content/full/123/1/e278
 33. Christensen RD, Yaish HM, Leon EL, Sola-Visner MC, Agrawal PB. A *de novo* T73I mutation in *PTPN11* in a neonate with severe and prolonged congenital thrombocytopenia and Noonan syndrome. *Neonatology*. 2013;104(1):1–5