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Original Article

Thrombocytopenia in Preterm Infants with Intrauterine Growth Restriction

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Sick preterm infants often have thrombocytopenia at birth, and this is often associated with intrauterine growth restriction (IUGR), or birth weights less than the 10th percentile. The pathogenesis of the thrombocytopenia and its importance in IUGR are still unclear. We studied the characteristics of preterm IUGR infants with thrombocytopenia. Twenty-seven singleton Japanese preterm IUGR infants were born between January 2002 and June 2007 at Okayama University Hospital. Infants with malformation, chromosomal abnormalities, alloimmune thrombocytopenia, sepsis, and maternal aspirin ingestion were excluded. The infants were divided into group A (n=8), which had thrombocytopenia within 72h after birth, and group B (n=19), which did not. There were significant differences in birth weight, head circumference, umbilical artery (UA)-pulsatility index (PI), middle cerebral artery-PI, UA-pH, UA-pO_2, and UA-pCO_2. The infants in group A were smaller, had abnormal blood flow patterns, and were hypoxic at birth. We speculate that the infants with thrombocytopenia were more severely growth-restricted by chronic hypoxia. Thrombocytopenia is an important parameter for chronic hypoxia in the uterine.

Key words: thrombocytopenia, intrauterine growth restriction, chronic hypoxia

Sick preterm infants are often thrombocytopenic, and thrombocytopenia occurs in 18-40% of all preterm infants admitted to neonatal intensive care units [1, 2]. Thrombocytopenia is often associated with intrauterine growth restriction (IUGR) [3, 4]. The thrombocytopenia in IUGR infants usually appears within 72h of birth and resolves within 1 week, and the platelet count rarely falls below $5\times10^4/\mu l$ [5, 6]. In contrast, thrombocytopenia in IUGR is related to intraventricular hemorrhage, preterm delivery, and so on [7]. In IUGR infants, impaired delivery of oxygen and other essential nutrients is thought to limit organ growth and musculoskeletal maturation. The cause of thrombocytopenia is also thought to be this hypoxia and low level of nutrients, but not all IUGR infants are thrombocytopenic. The pathogenesis of thrombocytopenia and its importance in IUGR are still unclear. Therefore, we studied the characteristics of preterm IUGR infants with thrombocytopenia.

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Materials and Methods

Between January 2002 and June 2007, 952 infants, including 246 preterm infants, were admitted to the neonatal intensive care unit at Okayama University Hospital. These included 27 singleton preterm infants with IUGR, or birth weights less than the 10th percentile for Japanese, and who had no malformations, chromosomal abnormalities, alloimmune thrombocytopenia, sepsis, or maternal aspirin ingestion within 4 weeks of delivery.

Generally, thrombocytopenia in full term infants is defined as a platelet count of less than $15\times10^4/\mu$l. According to the reports on the fetal platelet count of cord blood, the platelet count reaches $15\times10^4/\mu$l by the end of first trimester [8] and 17.5×10^4 to $25\times10^4/\mu$l by the end of the second trimester [9]. Therefore, thrombocytopenia in preterm infants is also defined as a platelet count of less than $15\times10^4/\mu$l at any gestational age. The platelet count of venous blood from the baby was analyzed at day 0 and 1. If it was below $15\times10^4/\mu$l or if it seemed to drop below $15\times10^4/\mu$l, we continue to check on it until the platelet count was over $15\times10^4/\mu$l. The infants were divided into 2 groups: group A (n=8) had thrombocytopenia within 72h after birth, and the remainder constituted group B (n=19).

Gestational age was calculated as the best obstetrical estimate according to the last menstrual period combined with a first-trimester ultrasound. Ultrasound scans were performed using 3.5- or 5-MHz probes (SSD 2200; Aloka, Tokyo, Japan). The data on the umbilical artery (UA)-pulsatility index (PI) and middle cerebral artery (MCA)-PI at the last measurement within 1 week before delivery were used. The definition of pregnancy-induced hypertension published by Japan Society of Obstetrics and Gynecology in 2005 was used. The mode of delivery vaginal delivery or cesarean section (C/S) was decided by monitoring indicative conditions such as abnormalities and fetal growth restriction. An umbilical artery gas analysis was performed immediately after birth. In this study, hypoglycemia was defined as a blood glucose level of less than 40mg/dl. The classification of intraventricular hemorrhage proposed by Papile *et al.* was used [10].

The Japanese standards for birth weight and head circumference (HC) published in 1998 and those for UA-PI and MCA-PI on fetal ultrasound published in 2003 were used. The PI was defined as (peak velocity−end-diastolic velocity)/mean velocity. As we could not find a good standard for placental weight for Japanese, we used data from Norway [11]. When analyzing the birth weight data, HC, UA-PI, MCA-PI, and placental weight, we considered the gestational age. We also analyzed the standard deviation (SD), presuming that each set of values was normally distributed.

The results are expressed as the mean ± SD or mean (range). The Mann-Whitney *U* test and Fisher's exact test were used to analyze the relationship between the 2 groups. Values of $p<0.05$ were considered statistically significant. The data were processed using StatView statistical software (SAS Institute, Cary, NC, USA). The study was approved by the ethics board at the Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences. All parents provided written informed consent upon entry into this study.

Results

The characteristics of the infants are shown in Table 1. The mean gestational age was 32.6 (28.1–35.7) weeks in group A and 33.9 (28.4–36.6) weeks in group B ($p=0.24$). There were no extremely premature babies who were born before 28 weeks. There was no difference in maternal age, primiparity ratio, gender, incidence of pregnancy-induced hypertension, C/S ratio, or Apgar score between the 2 groups.

The birth weight in group A, 1,167 (749–1,784) g, was significantly lower than that in group B, 1,572 (769–2, 248) g ($p=0.020$), and the SD in group A (-2.62 ± 0.80) was lower than that in group B (-1.95 ± 0.67) ($p=0.034$) (Fig. 1). The HC in group A, 27.2 (25.0–30.8) cm, was significantly smaller than that in group B, 29.2 (24.3–32.5) cm ($p=0.011$), as was the SD (-1.14 ± 0.58 vs. 0.40 ± 0.67, group A vs. group B; $p=0.012$) (Fig. 2). The placental weight in group A, 271 (180–368) g, tended to be lower than that in group B, 359 (180–550) g ($p=0.053$), although the SDs were not significantly different (-1.85 ± 0.52 vs. -1.33 ± 0.80, group A vs. group B; $p=0.094$).

The UA-PI in group A, 1.555 (0.878–2.121), was not significantly larger than that in group B, 1.132 (0.641–1.696) ($p=0.063$), although the SDs were

Table 1 Characteristics of the study infants

	Group A (n = 8)	Group B (n = 19)	*p*-value
Gestational age (weeks)	32.6 (28.1–35.7)	33.9 (28.4–36.6)	0.24
Maternal age	32.0 (19–41)	32.6 (23–39)	0.94
Primiparity	3 (37.5%)	10 (52.6%)	0.68*
Male	3 (37.5%)	8 (42.1%)	>0.99*
Pregnancy-induced hypertension	7 (87.5%)	9 (47.4%)	0.090*
C/S	8 (100%)	17 (89.5%)	>0.99*
Emergency C/S	4 (50%)	9 (47%)	>0.99*
Apgar score 1 minute	6.3 ± 1.8	7.5 ± 1.6	0.059
Apgar score 5 minutes	8.5 ± 0.9	8.8 ± 0.8	0.26
BW (g)	1167 (749–1784)	1572 (769–2248)	0.020
BW (SD)	−2.62 ± 0.80	−1.95 ± 0.67	0.034
HC (cm)	27.2 (25.0–30.8)	29.2 (24.3–32.5)	0.011
HC (SD)	−1.14 ± 0.58	0.40 ± 0.67	0.012
PW (g)	271 (180–368)	359 (180–550)	0.053
PW (SD)	−1.85 ± 0.52	−1.33 ± 0.80	0.094
BW/PW	4.35 ± 0.69	4.63 ± 1.52	0.98
UA-PI	1.555 (0.878–2.121)	1.132 (0.641–1.696)	0.063
UA-PI (SD)	4.27 ± 3.28	1.30 ± 1.60	0.028
MCA-PI	1.311 (1.016–1.637)	1.800 (1.229–2.434)	0.0010
MCA-PI (SD)	−1.90 ± 0.92	−0.24 ± 1.03	0.0011
UA-pH	7.246 ± 0.109	7.346 ± 0.061	0.026
UA-pO_2 (mmHg)	11.7 ± 3.8	16.3 ± 4.7	0.038
UA-pCO_2 (mmHg)	65.1 ± 16.6	48.3 ± 8.5	0.013
UA-BE (mmol/L)	0.65 ± 6.2	0.62 ± 4.6	0.85
UA-HCO_3 (mmol/L)	28.2 ± 5.2	26.4 ± 4.4	0.44
UA-lactate (mmol/L)	5.3 ± 2.2	3.6 ± 1.7	0.067
Platelets ($\times 10^4/\mu$l) (day 0)	14.3 ± 2.8	28.2 ± 7.4	0.0001
WBC (/μl) (day 0)	8169 ± 6512	9351 ± 4393	0.31
Hemoglobin (g/dl) (day 0)	17.6 ± 1.9	17.6 ± 2.1	0.54
Hypoglycemia	3 (37.5%)	4 (21%)	0.63*
IVH	0 (0%)	0 (0%)	>0.99*
NEC	0 (0%)	0 (0%)	>0.99*

There were significant differences in BW, HC, UA-PI, MCA-PI, UA-pH, UA-pO_2, UA-pCO_2, and platelet count, indicating that the infants in group A were more growth restricted and more hypoxic *in utero*.

*Fisher's exact test; the others, Mann-Whitney *U* test.

C/S, Cesarean section; BW, birth weight; HC, head circumference; PW, placental weight; UA, umbilical artery; PI, pulsatility index; MCA, middle cerebral artery; BE, base excess; WBC, white blood cells; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis.

4.27 ± 3.28 and 1.30 ± 1.60, respectively, for the 2 groups ($p = 0.028$) (Fig. 3). No infant had absent or reversed end-diastolic (ARED) flow in the umbilical artery. The MCA-PI in group A, 1.311 (1.016–1.637), was significantly smaller than that in group B, 1.800 (1.229–2.434) ($p = 0.0010$), as was the SD (−1.90 ± 0.92 vs. −0.24 ± 1.03, group A vs. group B; $p = 0.0011$) (Fig. 4).

The respective values of the umbilical artery gas analysis in groups A and B were as follows: UA-pH, 7.246 ± 0.109 vs. 7.346 ± 0.061; UA-pO_2, 11.7 ± 3.8 vs. 16.3 ± 4.7 mmHg; and UA-pCO_2, 65.1 ± 16.6 vs. 48.3 ± 8.5 mmHg ($p = 0.026$, 0.038, and 0.013, respectively). UA-pH and UA-pO_2 were lower and UA-pCO_2 was higher in group A compared with group B.

The platelet count at day 0 was significantly lower in group A than in group B ($14.3 \times 10^4 \pm 2.8 \times 10^4/\mu$l vs. $28.2 \times 10^4 \pm 7.4 \times 10^4/\mu$l; $p = 0.00010$). The platelet count in group A never dropped below $10 \times 10^4/\mu$l within 72 h after birth and had increased to more than $15 \times 10^4/\mu$l by day 9. There was no difference between the 2 groups in the white blood cell count or hemoglobin at day 0, and also no intergroup difference in the incidence of hypoglycemia. No infant had intraventricular hemorrhage or necrotizing enterocolitis.

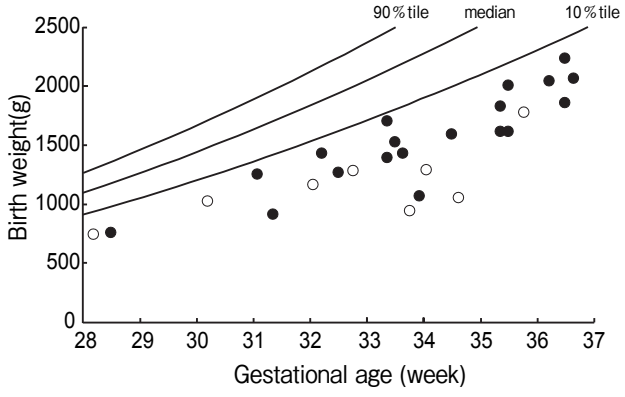

Fig. 1 Plot of individual birth weights versus gestational age. The infants with thrombocytopenia (group A, open circles) were smaller than the infants without thrombocytopenia (group B, filled circles) ($p=0.034$). The standard curves for males and multiparity are shown as references.

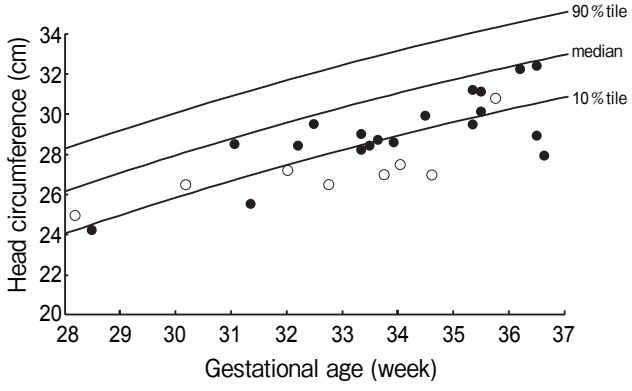

Fig. 2 Plot of individual head circumferences versus gestational age. The head circumferences of infants with thrombocytopenia (group A, open circles) were smaller than those of the infants without thrombocytopenia (group B, filled circles) ($p=0.012$). The standard curves for males are shown as references.

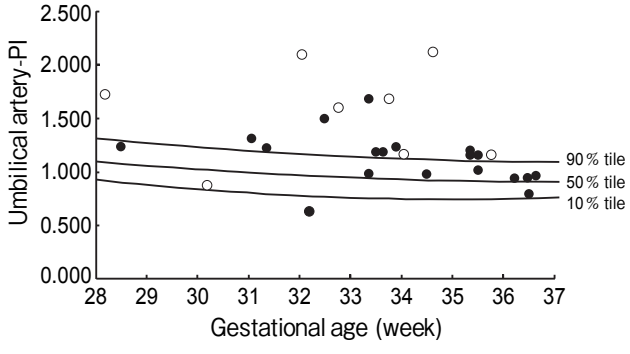

Fig. 3 Plot of the individual umbilical artery-pulsatility index values versus gestational age. The UA-PI of the infants with thrombocytopenia (group A, open circles) was higher than that of the infants without thrombocytopenia (group B, filled circles) ($p=0.028$). The standard curves are shown as references.

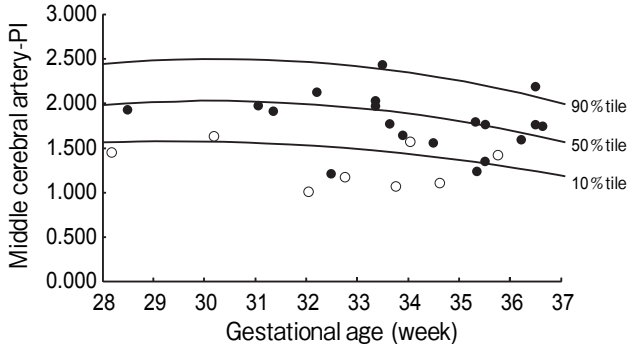

Fig. 4 Plot of the individual middle cerebral artery-pulsatility index values versus gestational age. The MCA-PI of the infants with thrombocytopenia (group A, open circles) was lower than that of the infants without thrombocytopenia (group B, filled circles) ($p=0.0011$). The standard curves are shown as references.

Discussion

The birth weight and HC of the infants with thrombocytopenia (group A) were significantly smaller than those of infants without thrombocytopenia (group B). In this study, all of the infants had IUGR, or weights less than the 10th percentile at birth. Therefore, this result indicated a strong relationship between thrombocytopenia and birth weight.

There are 2 types of IUGR: symmetrical and asymmetrical. Generally, symmetrical IUGR infants have a fetal factor such as a chromosomal anomaly, and birth weight and HC are reduced proportionately for the gestational age. By contrast, asymmetrical IUGR infants have maternal or placental factors such as pregnancy-induced hypertension or placental insufficiency. Fetal weight is reduced and brain growth is usually spared. The infants in the present study were considered to be asymmetrical, because we excluded cases with malformations and chromosomal abnormalities. Nevertheless, the smaller HC in group A indicates that the infants in group A were severely growth-restricted.

Blood flow analysis of UA and MCA is performed routinely and is used to evaluate fetal well-being [12]. Worsening of these indicators means circulatory failure, *i.e.*, oxygen supply breakdown [13–15]. Placental insufficiency causes inadequate gas exchange

[16]. With circulatory failure, UA-PI generally increases owing to the increased impedance of the placenta, while MCA-PI decreases due to the increased cerebral blood flow. In the present study, UA-PI was significantly higher and MCA-PI was lower in group A compared with group B, indicating that the infants in group A were chronically hypoxic. When ARED flow is recognized in the umbilical artery, the fetal cardiac output is severely redistributed secondary to hypoxia. Fetuses with ARED flow in the UA have a poor prognosis [17, 18]; however, there was no case with ARED in this study.

Platelets are initially produced mainly in the fetal liver, and the production site is transferred to the bone marrow in the third trimester [5]. The liver is the first organ to suffer the effects of growth restriction, because in hypoxia there is a decrease in blood flow to the liver, rather than an increase in blood flow to the ductus venosus [19]. It is not clear how chronic hypoxia affects progenitor cells and megakaryocytes in platelet production.

Umbilical artery gas analysis showed that the UA-pH and UA-pO_2 were lower and the UA-pCO_2 was higher in group A compared with group B. The UA gas analysis is influenced by the delivery method, but there were no differences in C/S, the emergency C/S ratio, or Apgar scores between the 2 groups. Nevertheless, the differences in the UA gas analysis showed that the infants in group A were hypoxic during delivery.

In summary, in the present study there were significant differences in birth weight, HC, UA-PI, MCA-PI, UA-pH, UA-pCO_2, and UA-pO_2 between the groups of infants with and without thrombocytopenia. Infants with thrombocytopenia were more severely growth-restricted by chronic hypoxia. Thrombocytopenia is an important parameter of chronic hypoxia in the uterine. Although there were no differences in short-term complications, the long-term complications in preterm IUGR infants with thrombocytopenia need to be studied.

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