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Clinical Presentation of Preterm Infants with Ventricular Septal Defect

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Ventricular septal defects (VSDs) are the most common congenital heart diseases; however, case reports of preterm infants with VSD are limited. The aim of this study is to share our experience with preterm infants with VSD and to record their short-term outcomes. Between January 2000 and December 2017, 32 preterm infants with VSD were admitted to our neonatal intensive care unit at gestational age < 32 weeks. Of these, 9 were excluded by exclusion criteria. The size and location of the VSD, details of treatment, and neonatal prognosis were retrospectively reviewed from the medical records. Among the 23 preterm infants, the median gestational age was 29.4 weeks (25.0-31.3 weeks) and the median birthweight was 924 g (524-1,526 g). There were 9 infants with VSD < 2 mm and 14 infants with VSD ≥ 2 mm. For the 9 infants with VSD < 2 mm, no medical or surgical treatments for VSDs were undertaken. Of the 14 infants with VSD ≥ 2 mm, 8 (57.1%) underwent medical and surgical treatment. Surgical treatment was performed more frequently in infants with VSD ≥ 2 mm than in those with VSD < 2 mm (P = 0.007). In preterm infants, the presence of VSD ≥ 2 mm increases the risk of surgical interventions and significant patent ductus arteriosus. It is important to encourage treatment for preterm infants with VSD ≥ 2 mm, including surgical interventions, in cooperation with pediatric cardiologists.

Keywords: patent ductus arteriosus; preterm infants; spontaneous closure; surgical intervention; ventricular septal defect
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Introduction

Congenital heart diseases (CHDs) are the most common congenital anomalies, occurring in approximately 6 to 10 infants per 1,000 live births (Reller et al. 2008; Khoshnood et al. 2012). Ventricular septal defects (VSDs) are the most common CHD in term infants (Hoffman 1995). The incidence of isolated VSD ranges from approximately 0.4 to 3.3 per 1,000 live births (Freedom et al. 1997). Term infants with isolated VSD usually have no symptoms during the neonatal period and gradually present with symptoms such as tachypnea, failure to thrive, and heart failure after the neonatal period (Rudolph 2009). The timing of symptom presentation is related to the size and location of the VSD.

Recently, medical treatments for newborn have progressed such that the survival rates of low birth weight infants, especially those with very low birth weight (VLBW), have significantly improved (Itabashi et al. 2009; Horbar et al. 2012; Kusuda et al. 2012). Several studies were reported regarding prevalence and outcomes of CHDs in preterm infants (Polito et al. 2013; Anderson et al. 2014). The most common CHD in preterm infants is also VSD (Kecskes and Cartwright 2002).

Nevertheless, case reports of preterm infants with VSD are limited. There are no data for preterm infants regarding the size at which a VSD becomes symptomatic and, therefore, requires surgical intervention. Hence, in this 18-year retrospective study, we summarized the clinical presentations of preterm infants with VSD in our neonatal intensive care unit (NICU) to characterize its symptoms and treatment course.

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Materials and Methods

Between January 2000 and December 2017, 1,124 preterm infants before 32 weeks of gestational age were admitted to our NICU in Kanagawa Children's Medical Center.

All preterm infants were examined using Doppler echocardiography (HP (SONOS 2000), iE33, EPIQ 7G; Philips, Andover, MA), including infants diagnosed with isolated VSD. Patients with co-existing preterm patent ductus arteriosus (PDA) and atrial septum defect were included in this study. We determined the treatment strategy in cooperation with pediatric cardiologists.

VSD size

The diameter of the VSD was measured using echocardiography with a four-chamber view, long-axis view, and short-axis view, and we adopted the maximum size of the VSD. In preterm infants, it was considered from clinical experience that VSD ≥ 2 mm was likely to develop complications; therefore, we divided VSDs into 2 groups according to the size of the defect: ≥ 2 mm and < 2 mm.

VSD location

We divided VSDs according to Kirklin's classification into 4 types: *subpulmonary* defects (Kirklin type I), *perimembranous* defects (Kirklin type II), *atrioventricular canal* defects (Kirklin type III), and *muscular* defects (Kirklin type IV) (Rudolph 2009).

Clinical findings and treatment

We gave medical treatment for clinical findings such as heart murmur, oliguria, edema, failure to thrive, effusion of carbon dioxide with pulmonary congestion, and dilated left atrium and left ventricle by echocardiography. We performed echocardiography at least 3 times daily during the acute phase.

Medical treatment included diuretic drug administration, mechanical ventilation, and water restriction. Surgical treatment included PDA ligation and pulmonary artery banding (PAB). When the effect of the medical treatment was insufficient, surgical interventions were performed.

Statistical analyses

Statistical analysis was performed using JMP Pro 13 (SAS; Cary, NC). Fisher's exact test was used to compare categorical variables, and the Mann-Whitney *U*-test was used to compare continuous variables. A $P < 0.05$ indicated statistical significance.

This study was approved by the ethical committee of the Kanagawa Children's Medical Center (No.1806-09). As this study was a retrospective observational study, informational disclosure was carried out during the opt-out process.

Results

Over 18 years, 32 preterm infants with VSD were admitted to our NICU within 5 days at gestational age of < 32 weeks. There were 9 patients excluded: 2 infants admitted after 5 days of age, 1 infant with trisomy 13, 3 infants with trisomy 18, and 3 infants with multiple malformation syndromes. We included 3 infants with trisomy 21 (Fig. 1). One patient (case 4) had aortic stenosis (AS) and a coronary-pulmonary artery (PA) fistula. The coronary-PA fistula has no hemodynamic effect on the patient, and he has not received any medical or surgical treatment for AS. Therefore, this patient was included in this study (Table 1).

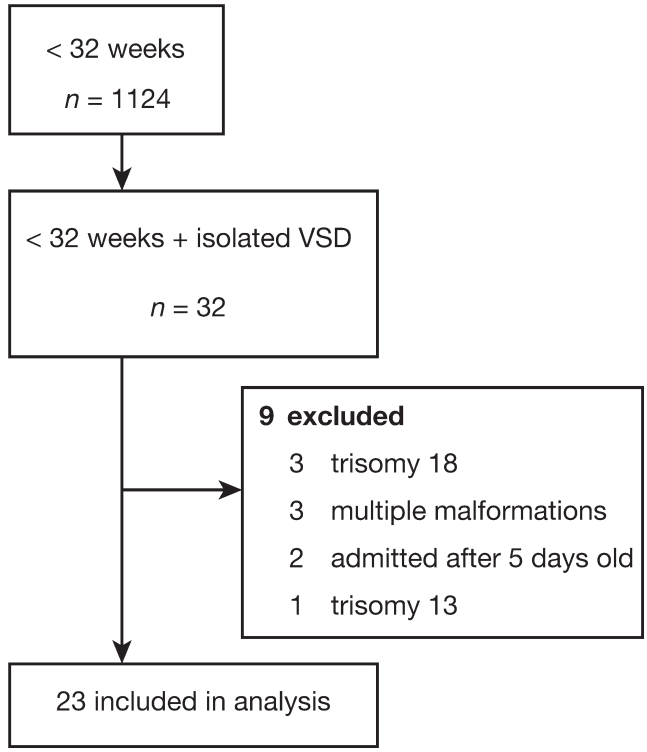

Fig.1. Study flow diagram.

Among 23 preterm infants, the median gestational age was 29.4 weeks (25.0-31.3 weeks) and the median birth weight was 924 g (524-1,526 g).

The diameter of the VSD was < 2 mm in 9 infants (39.1%), and it was ≥ 2 mm in 14 infants (60.9%).

Regarding the VSD location, 13, 8, and 2 patients had perimembranous VSD, muscular VSD, and both perimembranous and muscular VSDs, respectively. There were no infants with subpulmonary or atrioventricular VSDs.

Table 1 shows the details of 9 infants with VSD < 2 mm. Eight (88.9%) had muscular VSDs and 1 (11.1%) had a perimembranous VSD. None of the 9 infants received medical or surgical treatment for VSD. In several cases, VSDs that were smaller than 1 mm were too small to be accurately measured; these are described as "small" in the table. Spontaneous closure (SC) of the VSD was found in 7 (77.8%) infants. Six of 8 infants with muscular VSD developed SC and 1 infant with perimembranous VSD

Table 1. Nine infants with VSD < 2 mm.

Case	GA (weeks)	BW (g)	M/F	VSD type	VSD size (mm)	PDA	Complication (Morbidity)	Treatment for VSD	Outcome	Passage of VSD	Anomalies
1	25.7	690	F	Musc	small	Not symptomatic	None	None	Alive	SC at corrected 36W	None
2	27.3	784	F	Musc	small	Closed by Indo	None	None	Alive	SC at corrected 37W	None
3	27.6	1,306	F	Musc	small	SC	None	None	Alive	SC at corrected 37W	None
4	28.1	524	M	Musc	small	Closed by Indo	None	None	Alive	SC at corrected 45W	AS, coronary-PA fistula
5	28.1	746	M	Musc	small	Reopen after closed by Indo	None	None	Alive	SC at corrected 48W	Hypospadias
6	29.1	1,290	M	Musc	small	SC	None	None	Alive	SC at corrected 43W	None
7	29.4	1,322	F	Musc	small	Not symptomatic	None	None	Alive	Reduction at D/C, Not followed	Right aortic arch
8	29.7	638	F	P	1.5	SC	None	None	Alive	SC at corrected 36W	None
9	31.1	1,510	M	Musc	1	SC	None	None	Alive	Reduction at D/C, Not followed	None

AS, aortic stenosis; BW, birth weight; D/C, discharge; GA, gestational age; Indo, indomethacin; Musc, muscular; P, perimembranous; PA, pulmonary artery; PDA, patent ductus arteriosus; SC, spontaneous closure; VSD, ventricular septal defects; W, weeks.

Table 2. Non-surgical group of 6 infants with VSD ≥ 2 mm.

Case	GA (weeks)	BW (g)	M/F	VSD type size(mm)	PDA	Complication (Morbidity)	Treatment for VSD	Outcome	Passage of VSD	Anomalies
10	28.7	854	M	P (3.0)	Closed by Indo	None	Water restriction	Alive	Reduction at D/C, Not followed	None
11	29.3	1,169	M	P (3.0)	SC	None	MV	Alive	SC at corrected 5 months	None
12	29.6	1,415	F	P (3.5) + Musc (2.0)	SC	None	Diuretics + MV	Alive	SC at corrected 6 months	None
13	29.9	828	F	P (3.0)	SC	None	Diuretics + MV	Alive	SC at corrected 1 year	TTTS donor
14	30.1	888	M	P (5.0)	SC	NEC, PH	Diuretics + ACE inhibitor	Death	No change	Trisomy 21
15	31.1	1,526	F	P (3.5)	SC	None	none	Alive	Reduction at D/C, Not followed	None

ACE inhibitor, Angiotensin-Converting-Enzyme inhibitor; BW, birth weight; D/C, discharge; GA, gestational age; Indo, indomethacine; MV, mechanical ventilation; Musc, muscular; NEC, necrotizing enterocolitis; P, perimembranous; PDA, patent ductus arteriosus; PH, pulmonary hemorrhage; SC, spontaneous closure; TTTS, twin to twin transfusion; VSD, ventricular septal defects; W, weeks.

developed SC. The remaining 2 infants with muscular VSD were not followed-up because their VSDs were both reducing at discharge and asymptomatic.

Among 14 infants with VSD ≥ 2 mm, 1 infant (7.1%) received no treatment for VSD, 5 infants (35.7%) received only medical treatment, and 8 infants (57.1%) received medical and surgical treatment (Tables 2 and 3). Surgical intervention was more frequent in infants with VSD ≥ 2 mm than in those with VSD < 2 mm (P = 0.007).

The details of 6 infants with VSD ≥ 2 mm in the non-surgical group are shown in Table 2. Among 6 infants, the median gestational age was 29.7 weeks (28.7-31.1 weeks) and the median birth weight was 1,028 g (854-1,526 g). Medical treatment was performed for VSD in five of six infants (83.3%). Medical treatment included water restriction in 1 infant, mechanical ventilation in 1 infant, diuretic treatment, and mechanical ventilation in 2 infants, and both diuretic and angiotensin-converting-enzyme inhibitor in 1 infant. Five infants (83.3%) had no severe complications, however, 1 infant (16.7%) with trisomy 21 died. In this infant with trisomy 21, pulmonary hypertension was persistent, and the left-to-right shunt was minimal. Because of the worsening respiratory conditions, continuous positive airway pressure (CPAP) was started at 30 days of age. Two days later, he developed necrotizing enterocolitis (NEC) at corrected 34 weeks. He underwent intensive care including

Table 3. Surgical group of 8 infants with VSD ≥ 2 mm.

Case	GA (weeks)	BW (g)	M/F	VSD type size (mm)	PDA	Surgery (Day)	Complication (Morbidity)	Outcome	Passage of VSD and others	Anomalies
16	30.6	924	F	P (5.0)	Closed by Indo	PAB (D36)	None	Alive	Planning to radical operation	None
17	30.9	919	F	P (6.1)	Closed by Indo	PAB(D58)	None	Alive	Planning to radical operation	Trisomy 21
18	29.0	1,026	M	P (3.0)	Reopen after SC	PDA ligation +PAB(D3)	PH	Alive	SC at corrected 41W, PA debanding at corrected 3 months	None
19	31.1	873	M	P (5.0)	Not closed by Indo	PDA ligation +PAB(D20)	None	Alive	Performed radical operation at corrected 45W	Trisomy 21
20	31.3	1,197	F	P (5.0)	Reopen after closed by Indo	PDA ligation +PAB(D17)	None	Alive	Planning to radical operation	TTTS donor
21	25.0	800	M	P (2.5)	Reopen after closed by Indo	PDA ligation (D24)	IVH 3, PH	Alive	SC at corrected 35W	None
22	28.6	1,116	M	P (4.0)	Not closed by Indo	PDA ligation (D3)	IVH 1, PH	Alive	Performed radical operation at corrected 35W	DD twin
23	29.7	1,219	M	P (2.0) + Musc (1.5)	Not closed by Indo	PDA ligation (D4)	None	Alive	SC at corrected 44W	None

ACE inhibitor, Angiotensin-Converting-Enzyme inhibitor; BW, birth weight; D, day; D/C, discharge; GA, gestational age; Indo, indomethacine; IVH, intraventricular hemorrhage; Musc, muscular; NEC, necrotizing enterocolitis; P, perimembranous; PA, pulmonary artery; PAB, pulmonary artery banding; PDA, patent ductus arteriosus; PH, pulmonary hemorrhage; SC, spontaneous closure; TTTS, twin to twin transfusion; VSD, ventricular septal defect; W, weeks.

a colostomy procedure. Unfortunately, he developed pulmonary hemorrhage at corrected 36 weeks and died at 66 days of age (corrected 39 weeks).

The details of 8 infants with VSD ≥ 2 mm in the surgical group are shown in Table 3. Among the 8 infants, the median gestational age was 30.1 weeks (25.0-31.3 weeks) and the median birth weight was 975 g (800-1,219 g). No significant difference in gestational age and birth weight was observed between the surgical and non-surgical groups with VSD ≥ 2 mm (P = 0.846 and P = 0.796, respectively). Only pulmonary artery banding (PAB) was performed in 2 infants, both PAB and PDA ligation were performed in 3 infants, and only PDA ligation was performed in 3 infants. Six infants underwent PDA ligation. Three infants (37.5%) had severe complications. Two infants developed complications of both pulmonary hemorrhage and intraventricular hemorrhage (IVH), while 1 infant developed only pulmonary hemorrhage.

Of the 14 infants with VSD ≥ 2 mm, there were 6 cases that required surgery for significant PDA. Our study showed that preterm infants with VSD ≥ 2 mm were more likely to develop significant PDA than those with VSD < 2 mm (P = 0.048).

Among 14 infants with VSD ≥ 2 mm, SC of the VSD was found in 6 (42.9%) infants; 2 (14.3%) infants were not followed-up, because their VSDs were both reducing at discharge and asymptomatic. Radical operation for VSD has been or will be performed on 5 (35.7%) infants.

Discussion

Previous medical literature regarding preterm infants with VSD is limited. Pappas et al. (2012) reported CHD in extremely low birth weight (ELBW) infants and the most common CHD seen in ELBW was VSD (18%). In this study, we showed that preterm infants with VSD < 2 mm did not require treatment for VSD, and those with VSD ≥ 2 mm required surgical treatment, including PDA ligation because they were more likely to develop complications such as PDA.

Significant PDA predisposes preterm infants to serious morbidity and mortality (Sellmer et al. 2013). We discovered that 3 out of 6 infants that required PDA ligation had severe preterm complications (Table 3). Prompt surgical intervention, such as PDA ligation or PAB, should be considered in preterm infants with PDA because they worsen rapidly due to pulmonary hemorrhage or NEC. It has been previously reported that atrial natriuretic peptide (ANP) dose-dependently reopens the constricted postnatal ductus arteriosus in rat pups (Toyoshima et al. 2007). The increased ANP and brain natriuretic peptide (BNP) levels, accompanying the VSD, may delay closure of the ductus arteriosus. We speculate that increased ANP and BNP levels, accompanying the VSD in preterm infants, may further delay the closure of the ductus arteriosus. Therefore, studies must be conducted in the future to evaluate whether the ductus arteriosus in human neonates is open when ANP and BNP levels increase.

Surgical interventions for VSDs have been required in

term infants if the size of the defect is > 5 mm in diameter (Hamaoka et al. 2019). Itabashi et al. (2014) reported Japanese neonatal anthropometric charts for gestational age; when we considered differences in sex and primiparous or multiparous births at 40 weeks, the average birthweight and body length were 3,106 g and 49.4 cm, respectively. We calculated the body surface area (BSA) of Japanese term infants from the report, obtaining a value of 0.197 m^2. We decided to seek surgical interventions for preterm infants based on the BSA of our target infants. BSA was calculated using the DuBois formula (BSA = 0.007184 *$Height_{cm}^{0.725}$ *$Weight_{kg}^{0.425}$).

The BSA of the 23 infants, calculated from the median birthweight and height, was 0.0976 m^2. When compared by BSA, 5 mm defects in term infants corresponded with 2.48 mm in preterm infant cases. However, defect size was not our only criterion for surgical intervention. We decided to proceed with surgical intervention based on a comprehensive assessment, including hemodynamics. Based on our clinical experience, we divided VSDs into 2 groups: ≥ 2 mm and < 2 mm. We found significant differences in surgical intervention between these groups. We had initially planned on comparing the size of aortic annulus dimension and defect; however, the records were missing the size of aortic annulus dimension.

In term infants with large VSDs, the patient develops increasing respiratory distress and failure to thrive. The progression of symptoms varies, and some infants may develop severe cardiac failure within 4 to 6 weeks after birth. By comparison, the onset of cardiac failure is frequently noted within 1 to 2 weeks after birth in preterm infants with VSD (Rudolph 2009). This is probably related, at least in part, to the fact that pulmonary vascular reactivity is not as well developed in the preterm infant, and thus, pulmonary vascular resistance may not be sustained as in the mature infant. Another important consideration in the preterm infant is the high level of oxygen consumption in relation to body weight, because the preterm infant has a large surface area relative to body weight. Therefore, the requirement for cardiac output to provide oxygen to systemic tissues is greater and a larger load would be placed on the left ventricle (Rudolph 2009). Furthermore, approximately 24 hours after birth, the pulmonary vascular resistance decreases and the shunt flow through the ductus arteriosus increases. Accordingly, the preload increases rapidly; however, the left ventricle of the preterm infant is known to have low distensibility (Friedman 1972; Romero and Friedman 1979). Therefore, in preterm infants, the preterm heart cannot accept large volumes of blood, which results in an increase in the pulmonary venous pressure and venous congestion. Pulmonary congestion may occur even when the left ventricle is exposed to a relatively small increase in preload, indicating that the preload reserve is limited in the preterm infants (Toyoshima et al. 2013). In preterm infants, because they develop cardiac failure earlier, it is important to consider treatment promptly.

With regards to SC of VSD, Li et al. (2016) reported the frequency of cases in which VSD was diagnosed during the fetal period, and SC was confirmed within the first 2 years of life. According to this report, SC occurred in 42.8% of patients during gestation and within the first 2 years of life; birth weight and defect meter showed significant differences between the three groups (SC during gestation, SC after birth, and persistent VSD). In our cases, we found that 77.8% of the SCs of VSDs in the VSD < 2 mm group and 42.9% in the VSD ≥ 2 mm group. SC was mainly observed in the VSD < 2 mm group in our study. In preterm infants, despite spontaneous closure of the VSD (such as in case 18), preterm complications such as pulmonary hemorrhage occurred and PAB was required. Therefore, we need to be careful when treating preterm infants with VSD.

We included infants with trisomy 21 in this study. Trisomy 21 is found to have a long-term survival of approximately 60 years on average with current medical care (Zigman 2013). Therefore, in this study we included infants with trisomy 21 but excluded infants with trisomy 13 and trisomy 18 because of their short life span. In the infant that died, left-to-right shunt was minimal after birth because of persistent pulmonary hypertension associated with trisomy 21 (Shah et al. 2004; Cua et al. 2007; Weijerman et al. 2010; Martin et al. 2018). Pulmonary hypertension was attenuated with improvement of oxygenation by using CPAP and left-to-right shunt increased. As a result, he developed NEC at corrected age of 34 weeks.

Our study had some limitations. First, on echocardiography, we often cannot observe the left-to-right shunt in the immediate postnatal period with residual physiological pulmonary hypertension; therefore, it is difficult to measure the correct size of the VSD in the immediate postnatal period. However, the final diagnosis was achieved along with pediatric cardiologists to be as accurate as possible. Second, among VSDs < 2 mm, 88.9% (8 of 9 cases) were muscular, while all VSDs ≥ 2 mm (14 cases) were perimembranous. Because we did not consider the differences in the locations of the VSDs in this study, we cannot disregard the possibility that the difference in symptoms may be due to the location of the VSD in addition to its size. However, according to the available literature, the hemodynamic effects of VSD after birth in term infants are markedly associated with two factors, namely, size of the defect and relative outflow resistances of the right and left ventricles. The location of the defect is not of particular importance in determining the amount of shunting or the clinical consequences (Rudolph 2009).

In conclusion, in preterm infants, the presence of VSD ≥ 2 mm increases the risk of PDA and is likely to cause severe premature complications including pulmonary hemorrhage, IVH, and NEC. It is important to promote treatment for preterm infants with VSD, including surgical intervention, in cooperation with pediatric cardiologists.

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Conflict of Interest

The authors declare no conflict of interest.

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