Cardiology in the Young

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Characteristics of the pulmonary circulation in infants with complete atrioventricular septal defect

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Abstract

Objective: Infants with complete atrioventricular septal defect occasionally accompany pulmonary hypertension; however, the pulmonary circulation can be altered by pulmonary vascular conditions as well as the left heart lesions. This study aimed to explore whether the left heart lesions were related to the pulmonary circulation among them. *Methods:* We performed echocardiography and cardiac catheterisation in 42 infants with complete atrioventricular septal defect and studied relationships between the pulmonary haemodynamic parameters and the left heart morphology. *Results:* Age and weight at preoperative evaluation were 65 days (47-114) (the median following interquartile range) and 5.5 kg (4.0-7.1), respectively. There were 27 individuals with Down syndrome. Gestational age was 38 weeks (37-39). Catheterisation showed mean pulmonary arterial pressure: 36 (29-46) mmHg, the ratio of pulmonary to systemic blood flow: 3.45 (2.79-4.98), pulmonary vascular resistance: 2.20 Wood units·m^2 (1.53-3.65), and pulmonary arterial compliance: 2.78 (1.86-4.10) ml/Hg/m^2. Echocardiography showed the Rastelli classification type A in 28 and type C in 14, moderate or severe left atrioventricular valve regurgitation in 19 patients (45%), atrioventricular valve index of 0.67 (0.56-0.79), left ventricular end-diastolic volume z score of 4.46 (1.96-7.78), and aortic valve diameter z score of −0.70 (−1.91 to 0.20). Multivariable regression analysis revealed that preoperative pulmonary vascular resistance was significantly correlated to gestational age ($p = 0.002$), and that preoperative pulmonary arterial compliance was significantly correlated to gestational age ($p = 0.009$) and Down syndrome ($p = 0.036$). *Conclusions:* The pulmonary circulation does not depend upon the presence of left heart lesions but gestational age and Down syndrome in infants with complete atrioventricular septal defect.

Complete atrioventricular septal defect is characterised by large interatrial and interventricular septal defects and the common atrioventricular valve that spans the entire septal defect.[1] Tachypnea, feeding difficulty, and failure to thrive invariably occur during early infancy as a result of excessive pulmonary blood flow; however, these clinical manifestations are confounded by the postnatal condition of the pulmonary vasculature, atrioventricular valve regurgitation and/or stenosis, and left and/or right ventricular outflow obstruction. Therefore, the pulmonary circulation should be comprehensively evaluated in infants with complete atrioventricular septal defect.

When we discuss the pulmonary circulation, it is critical to assess the following two parameters: pulmonary vascular resistance, which refers to the resistance encountered by blood as it flows through the pulmonary vasculature, and pulmonary arterial compliance, which refers to the elasticity and extensibility of vessels. There is a unique hyperbolic relationship between pulmonary vascular resistance and arterial compliance, and their coupling reflects the condition of the pulmonary vasculature. Previous studies have shown that pulmonary arterial compliance is a powerful predictor for outcomes in children with idiopathic/hereditary pulmonary arterial hypertension, and in those with pulmonary hypertension associated with congenital heart disease.[2-5]. However, pulmonary arterial compliance can be influenced by age, the amount of left-to-right shunt, and left ventricular function.[6] Recent studies also have shown that precapillary and postcapillary pulmonary hypertension coexist among patients with pulmonary arterial hypertension associated with the left heart disease, and that lower pulmonary arterial compliance is correlated with poor outcomes among them.[7-10] However, there is little information about the pulmonary circulation with left heart lesions in infants with complete atrioventricular septal defect. Therefore, this retrospective cohort study aims to establish whether left heart lesions, including atrioventricular valve morphology, are related to the pulmonary circulation in such patients.

Methods

Patients

This study was approved by the Institutional Ethics Committee of the Hospital. Informed consent was obtained from all patients or their guardians. Between 2000 and 2018, a total of 72 patients with complete atrioventricular septal defect were admitted to our hospital. We excluded patients with unbalanced ventricles who had undergone functionally univentricular repair, patients with right ventricular outflow obstruction such as tetralogy of Fallot, and patients with an arch anomaly such as aortic coarctation. Patients with patent ductus arteriosus, regardless of size, were included. As per our institutional standard clinical practice protocol, cardiac catheterisation is indicated before and after corrective surgery to confirm the improvement of pulmonary hypertension in children with complete atrioventricular septal defect. Pulmonary hypertension was defined as mean pulmonary arterial pressure more than 20 mmHg, or the ratio of pulmonary to systemic mean pressure more than 0.30.[11,12] We retrospectively obtained right heart catheter measurements from clinical records before and after corrective surgery. Corrective surgery was usually carried out during infancy, and staged repair via pulmonary arterial banding was preferred in symptomatic neonates with complete atrioventricular septal defect.

Echocardiography and cardiac catheterisation

Standard echocardiography was performed before corrective surgery according to the guideline of the American College of Echocardiography.[13] In addition, atrioventricular valve morphology was classified based on morphology of the superior bridging leaflet (i.e., the Rastelli classification). We also calculated the atrioventricular valve index derived by the left atrioventricular valve area divided by the total atrioventricular valve area.[14] Atrioventricular valve regurgitation was also assessed by colour Doppler echocardiography and classified into mild, moderate, and severe. The aortic valve diameter was measured from hinge-point to hinge-point. All measurements were evaluated and validated by at least two out of three observers (H.D., R.M., and H.E.).

Cardiac catheterisation was performed approximately 1 month prior to surgery to evaluate pulmonary haemodynamics. With patients in the supine position, standard techniques were utiliaed to measure all catheteriaation parameters under fluoroscopic guidance. Thiamylal sodium or midazolam was used for sedation. All patients were examined when breathing in room air without oxygen supplementation or intubation. Pressures were measured at the end of expiration using a Berman angiographic catheter or a Swan-Ganz catheter (Gadelius Medical K. K., Tokyo, Japan). If possible, left atrial pressure was measured through an atrial communication. Otherwise, pulmonary capillary wedge pressure was measured to calculate the transpulmonary pressure. Pulmonary hypertension was confirmed if the mean pulmonary arterial pressure was >20 mmHg. Pulmonary blood flow was calculated based on the Fick principle, which is based on the measurements of arteriovenous difference of oxygen content and oxygen consumption. We used assumed oxygen consumption of 180 ml/minute/m^2. Pulmonary vascular resistance was calculated as the difference between mean pulmonary arterial pressure and left atrial pressure, or pulmonary arterial capillary wedge pressure divided by pulmonary blood flow. Pulmonary stroke volume was calculated as pulmonary blood flow divided by heart rate during the examination. Pulmonary arterial compliance was calculated as pulmonary stroke volume divided by pulmonary arterial pulse pressure (the difference between systolic and diastolic pulmonary arterial pressures). Resistance–compliance time was calculated as the product of pulmonary vascular resistance and arterial compliance. The left ventricular end-diastolic volume was measured by the Simpson's method based on a left ventriculogram, and was expressed as a z score. Arterial oxygen partial pressure was measured in the cardiac catheterisation laboratory. An acute pulmonary vasodilator test was performed using inhaled oxygen and/or nitric oxide when the calculated pulmonary vascular resistance was more than 4 Wood units·m^2. A decrease in the mean pulmonary arterial pressure or resistance >20%, without a decrease in cardiac output, was interpreted to be a positive pulmonary vasodilator test.[15]

Statistical analysis

Statistical analysis was performed using the Analysis ToolPak add-on for Microsoft Office Excel™ (BellCurve, Tokyo). Values were expressed as the median following the interquartile ranges. We compared variables including arterial oxygen partial pressure, systolic and mean pulmonary arterial pressure, left atrial pressure or pulmonary arterial wedge pressure, the ratio of pulmonary to systemic pressure ratio, the ratio of pulmonary to systemic blood flow, pulmonary vascular resistance, pulmonary arterial compliance, and resistor-compliance time before and after corrective surgery using Wilcoxon signed-rank test. We also performed multivariable linear regression analysis as the objective variables of pre-/postoperative pulmonary vascular resistance and arterial compliance, and the predictor variables of age, sex, gestational age, Down syndrome, the Rastelli classification (type C), atrioventricular valve index, the presence of left atrioventricular valve regurgitation (moderate or severe), z scores of left ventricular end-diastolic volume and the aortic valve diameter, the left ventricular ejection fraction, and arterial oxygen partial pressure. For all statistical analysis, p-values of <0.05 were considered statistically significant.

Results

Among 72 patients with complete atrioventricular septal defect who were admitted to our hospital during the study period, we excluded 14 patients with unbalanced ventricles who underwent univentricular repair, 10 patients with right ventricular outflow obstruction, 4 patients with an arch anomaly, and 2 patients who did not undergo corrective surgery. Thus, a total of 42 patients with complete atrioventricular septal defect were studied. Patients' characteristics are shown in Table 1. Age and weight at the first evaluation were 65 days (47-114) and 3.6 kg (3.2-4.6), respectively. There were 19 males (45%) and 27 individuals with Down syndrome (64%). Gestational age and birth weight were 38 weeks (37-39) and 2.8 kg (2.7-3.0), respectively. There were 28 patients who underwent primary corrective repair and 14 patients who underwent staged repair via pulmonary arterial banding. Age and weight at corrective surgery were 6 months (3-14) and 5.5 kg (4.0-7.1), respectively. Postoperative cardiac catherisation was performed at the age of 7 months (3-14).

Haemodynamic data is shown in Table 2. Rastelli classification type A anatomy was seen in 28 infants and type C in 14, with moderate or severe left atrioventricular valve regurgitation in 19 patients. Atrioventricular valve index, z score of left ventricular end-diastolic volume, ejection fraction, and z score of the aortic valve diameter were 0.67 (0.56-0.79), 4.46 (1.96-7.78), 63 % (58-67), and −0.70 (−1.91 to −0.20), respectively. Preoperative pulmonary catherisation showed arterial oxygen partial pressure of 67 mmHg (58-76), mean pulmonary arterial pressure of 36 mmHg (29-46), the ratio of pulmonary

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Table 1. Patients' characteristics of 42 patients with complete atrioventricular septal defect

	n = 42
Age at first evaluation, days	65 (47-114)
Weight at first evaluation, kg	3.6 (3.2-4.6)
Sex, male	19 (45%)
Gestational age, weeks	38 (37-39)
Birth weight, kg	2.7 (2.63)
Down syndrome	27 (64%)
Age at corrective repair, months	6 (3-14)
Weight at corrective repair, kg	5.5 (4.0–7.1)
Staged repair, n	14 (33%)
Age at postoperative evaluation, months	7 (3-14)
Weight at postoperative evaluation, kg	5.4 (4.2-7.2)

Continuous values are expressed as the median follow by the interquartile rage
Category values are expressed as a number following the percentage
cAVSD: complete atrioventricular septal defect

to systemic blood flow of 3.45 (2.79-4.98), pulmonary vascular resistance of 2.20 Wood units·m^2 (1.53-3.65), pulmonary arterial compliance of 2.78 ml/mmHg/m^2 (1.86-4.10), and resistor-compliance time of 0.39 seconds (0.34-0.46). Pulmonary hypertension was identified in all patients. There were 15 patients with pulmonary vascular resistance more than 3 Wood units·m^2 who were categorised as having pulmonary arterial hypertension. Acute pulmonary vasodilator tests were performed in six preoperative patients, and positive responses were found in three of them. Postoperative cardiac catheterisation showed an arterial oxygen partial pressure of 79 mmHg (73-85), mean pulmonary arterial pressure of 18 mmHg (14-24), pulmonary vascular resistance of 2.61 Wood units·m^2 (1.97-4.24), pulmonary arterial compliance of 1.79 ml/mmHg/m^2 (1.32-2.51), and resistor–compliance time 0.32 seconds (0.25-0.36), which suggested that all pulmonary haemodynamic parameters except pulmonary vascular resistance were significantly decreased after corrective surgery. Further, preoperative pulmonary vascular resistance, pulmonary arterial compliance, and resistor-compliance time were proportionally correlated with postoperative pulmonary vascular resistance ($r = 0.61$, $p < 0.001$), pulmonary arterial compliance ($r = 0.692$, $p < 0.001$), and resistor–compliance time ($r = 0.424$, $p = 0.006$), respectively. There was a hyperbolic relationship between pulmonary vascular resistance and arterial compliance obtained by preoperative and postoperative cardiac catheterisation (Fig 1).

Multivariable regression analysis revealed that preoperative pulmonary vascular resistance was significantly correlated to gestational age (coefficient: 0.78, 95% confidential interval: 0.30-1.25, $p = 0.002$).Preoperative pulmonary arterial compliance was both significantly correlated to gestational age (coefficient: −0.96, 95% confidential interval: −1.66 to 0.25, $p = 0.009$) and Down syndrome (coefficient: −2.38, 95% confidential interval: −4.61 to 0.15, $p = 0.036$) (Fig 2). The Rastelli classification, atrioventricular valve index, the degree of atrioventricular valve regurgitation, z score of left ventricular end-diastolic volume, ejection fraction, and z score of the aortic valve diameter were not related to pre-/postoperative pulmonary vascular resistance or pulmonary arterial compliance. Postoperative pulmonary arterial compliance tended to be associated with gestational age, Down syndrome, and the degree of left atrioventricular valve regurgitation, but did not reach statistical significance.

Discussion

The major finding of our study was that the pulmonary circulation mainly does not depend upon left heart lesions but gestational age and Down syndrome in infants with complete atrioventricular septal defect. The measurement of pulmonary arterial compliance has recently gained interests in patients with pulmonary hypertension associated with congenital heart disease, because pulmonary arterial compliance consistently predicts mortality compared to pulmonary vascular resistance in patient with different causes of pulmonary hypertension.[2-10] In infants with ventricular septal defect and pulmonary hypertension, pulmonary vascular resistance and arterial compliance were reported to range from 1.6 to 3.2 Wood unit·m^2 and from 2.0 to 3.3 ml/mmHg/m^2, respectively which was consistent with our present study.[3] Pulmonary arterial compliance less than 2.15 ml/mmHg/m^2 is an optimal cut-off value to predict poor prognosis in patients with left heart disease and pulmonary hypertension,[16] and pulmonary arterial compliance less than 2.50 ml/mmHg/m^2 predicts high postoperative pulmonary arterial pressure in infants with ventricular septal defect and pulmonary hypertension.[3] It is also known that pulmonary arterial compliance can be altered by pulmonary arterial vasoconstriction linked to individual characteristics of endothelial function and smooth muscle cells in patients with pulmonary hypertension due to left heart disease.[17] However, our results demonstrated that left heart lesions were not related to pre-/postoperative pulmonary vascular resistance and arterial compliance in infants with complete atrioventricular septal defect.

We identified that younger gestational age was an independent factor associated with high preoperative pulmonary vascular resistance and low preoperative pulmonary arterial compliance in patients with complete atrioventricular septal defect. Previous studies have shown that individuals with preterm birth have a modestly high blood pressure throughout their lives, and that preterm birth is linked to an increased risk of pulmonary hypertension.[18,19] The development of the pulmonary vasculature is closely related to the airways and its branching morphogenesis, which can be affected by prematurity.[20] The maldevelopment of pulmonary vasculature in preterm infants results in a reduced number of recruitment capillaries. Our previous study showed that preterm infants with pulmonary hypertension and ventricular septal defect had lower pulmonary arterial compliance compared to full-term infants, and that there was a distinct difference in resistance–compliance coupling between preterm and full-term infants.[21] Capillary rarefaction, or a reduced number of recruitment capillaries, is supposed to play a key role during fetal and the early neonatal period in preterm infants. The present study also suggested that younger gestational age contributed to pulmonary hypertension probably due to an alteration of capillary rarefaction in preterm infants with complete atrioventricular septal defect.

In addition, we revealed that Down syndrome was an independent factor relevant to low preoperative pulmonary arterial compliance in infants with complete atrioventricular septal defect. In individuals with Down syndrome, the pathophysiology behind pulmonary hypertension is diverse, including left-to-right shunt due to congenital heart disease, alveolar hypoxia due to chronic airway obstruction, impaired vascular and alveolar growth disrupted by angiogenesis during development, a decreased number of branches and capillaries, histological characteristics of poor thickening of the tunica media resulting in high shear stress to the pulmonary arterial media, and an imbalance of prostacyclin to thromboxane production resulting in platelets aggregation, cell

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Table 2. Echocardiographic and cardiac catheterisation data

	Preoperative (n = 42)		Postoperative (n = 42)		p
Left side lesions					
Rastelli classification	A: 28, C: 14				
Left AVV regurgiation, moderate	19	(0.56–0.79)	14		0.26
AVV index	0.67	(1.96–7.78)			
LVEDV, z score	4.46	(58–67)	2.48	(0.29–3.87)	0.17
LVEF, %	63	(58–76)	61	(58–65)	0.13
AVD, z score	−0.70	(−1.91 to −0.20)			
Pulmonary haemodynamics					
PaO_2, mmHg	67	(50–71)	79	(73–85)	<0.0001
Systolic PAP, mmHg	57	(50–71)	30	(25–39)	<0.0001
Mean PAP, mmHg	36	(29–46)	18	(14–24)	<0.0001
LAP, mmHg	4	(3–6)	8	(5–9)	<0.0001
Pp/Ps	0.80	(0.66–0.92)	0.34	(0.26–0.39)	<0.0001
Qp/Qs	3.45	(2.79–4.98)			
Rp, Wood units m^2	2.20	(1.53–3.65)	2.61	(1.97–4.24)	0.076
Cp, ml/mmHg/m^2	2.78	(1.86–4.10)	1.79	(1.32–2.51)	<0.0001
RC time, seconds	0.39	(0.34–0.46)	0.32	(0.25–0.36)	<0.0001

AVV: atrioventricular valve, LVEDV: left ventricular end-diastolic volume, LVEF: left ventircular ejection fraction, AVD: aortic valve diameter, PaO2: partial pressure of arterial oxygen, PAP: pulmonary arterial pressure, Pp/Ps: the ratio of pulmonary to systemic pressure, Qp/Qs: the ratio of pulmonary to systemic blood flow, Rp: pulmonary arterial resistance, Cp: pulmonary arterial compliance, RC time: resistance–compliance time

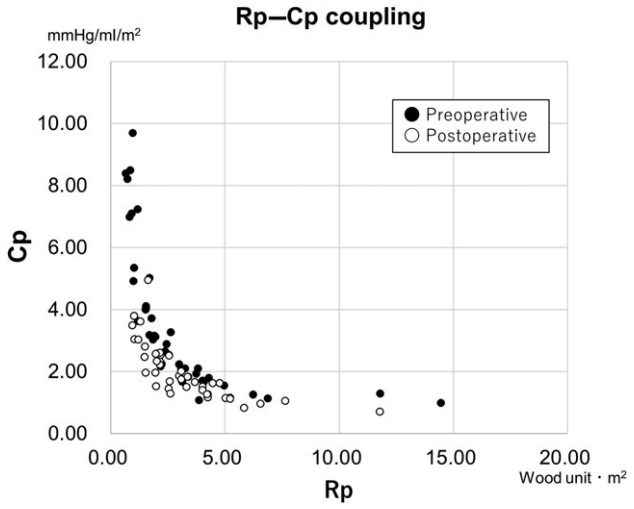

Figure 1. Plots of pulmonary arterial resistance against pulmonary arterial compliance demonstrating a hyperbolic relationship. Closed and open circles mean preoperative and postoperative data, respectively.

proliferation, and vasoconstriction.[22,23] These distinct features of the pulmonary vasculature in individuals with Down syndrome lead to a reduction in capillary recruitment, ensuring a downward-shifted resistance–compliance coupling curve.[23] Therefore, patients with congenital heart disease and Down syndrome occasionally develop severe pulmonary hypertension despite successful corrective cardiac surgery, and require several medications for postoperative pulmonary hypertension.

We found that preoperative pulmonary vascular resistance and arterial compliance were proportionally correlated with postoperative pulmonary vascular resistance and arterial compliance. Patients with low pulmonary arterial compliance, especially patients with Down syndrome, are likely to be susceptible to pulmonary vascular obstructive disease; therefore, if corrective surgery is delayed, they could develop irreversible postoperative pulmonary hypertension due to the development of pulmonary vascular obstructive disease. Although we performed corrective surgery at the median age of 7 months as standard management, patients with preoperative low pulmonary arterial compliance should be offered corrective surgery at a younger age. It is possible that pulmonary arterial compliance is a useful parameter to know when planning optimal timing for corrective surgery.

This study has some limitations. First, our cohort consisted of a small number of patients. Further, it was susceptible to information bias because this was a retrospective observational study. Postoperative pulmonary arterial compliance tended to be associated with gestational age, Down syndrome, and the left atrioventricular valve regurgitation. However, there was no significant correlation found due to the small sample size. Unfortunately, data regarding long-term follow up was not available because the majority of patients were followed in other institutions. We hope to undertake a further study regarding long-term outcomes. Second, there are two methods to calculate total pulmonary arterial compliance: the pulse pressure method and the exponential decay of diastolic pulmonary arterial pressure wave method. We chose the pulse pressure method to calculate total pulmonary arterial compliance pulmonary arterial compliance using the parameters available from right heart catheterisation. It is unclear if using the other method would have altered the results. Third, pulmonary arterial compliance

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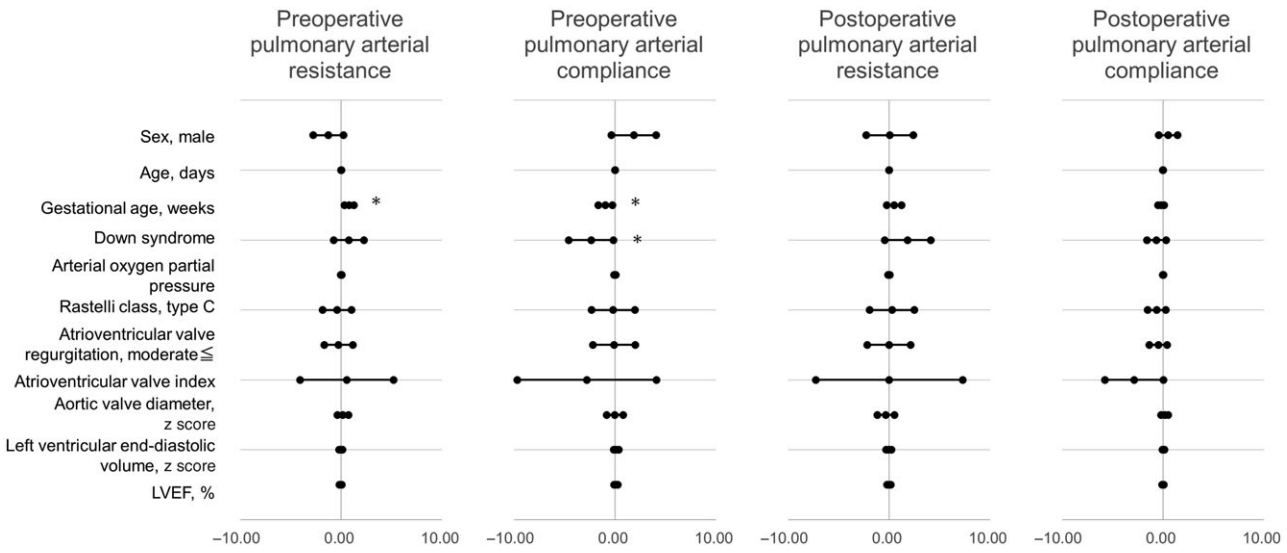

Figure 2. Forrest plots of multivariable liner regression analysis are shown. Preoperative pulmonary arterial resistance is significantly related to gestational age, while preoperative pulmonary arterial compliance is significantly related to gestational age and Down syndrome. Asterisks mean statistical significance.

was decreased after corrective surgery. As we performed postoperative cardiac catherisation within a month after corrective surgery, the sustained increase of inflammatory cytokines or pulmonary vasoconstrictive substances such as endothelin-1 might lead to abnormal pulmonary vasoconstriction, resulting in a decrease in postoperative pulmonary arterial compliance.

Conclusion

A hyperbolic relationship between pulmonary vascular resistance and arterial compliance was universally observed in infants with complete atrioventricular septal defect and pulmonary hypertension. Despite the significance of atrioventricular valve morphology and the degree of atrioventricular valve regurgitation, the pulmonary vascular resistance and arterial compliance are not associated with left sided lesions if the patients had corrective surgery in a timely manner. The pulmonary arterial compliance was related to gestational age and Down syndrome.

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Conflicts of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committees of Kyushu Hospital, Japan Community Healthcare Organization.

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