Clinical Characteristics and Prognosis of Fetal Left Ventricular Noncompaction in Japan

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Background: Left ventricular noncompaction (LVNC) is morphologically characterized by numerous prominent trabeculations and a severely thickened, two-layered myocardium. The fetal onset of LVNC has rarely been described.

Methods and Results: We conducted nationwide retrospective surveys on fetal cardiomyopathy (CM) in Japan from 2010 to 2016, from which 38 fetal patients with CM were enrolled, including 16 patients with LVNC. The rate of diagnostic concordance was 56.3% between fetal and postnatal visits in LVNC patients. The increase in the ratio of noncompacted to compacted (N/C) myocardium was time-dependent throughout the fetal period till birth (LV lateral: 1.6 ± 0.1 to 2.8 ± 0.2 ; LV apex: 2.0 ± 0.1 to 3.2 ± 0.2). Of all fetuses, 16 (42.1%) died or underwent heart transplantation (HT), with 3 intrauterine deaths. Lower fetal cardiovascular profile score (odds ratio, 26.9; $P=0.0266$) was a risk factor for death or HT. N/C ratio ≥ 1.6 at the apex at the first visit was a significant predictor of LVNC (odds ratio, 47.8; $P=0.0113$).

Conclusions: This is the first study to reveal the etiology of fetal CM based on results from a nationwide survey in Japan, highlighting the difficulty of diagnosing LVNC in fetal patients. To better understand and manage fetal CM, novel diagnostic criteria of LVNC in fetus should be established.

Key Words: Cardiovascular profile score; Fetal echocardiography; Left ventricular noncompaction; N/C ratio

Left ventricular noncompaction (LVNC) is morphologically characterized by a severely thickened, two-layered myocardium and numerous prominent trabeculations and deep intertrabecular recesses that communicate with the LV cavity.¹ The clinical features of LVNC are highly variable: some patients experience no symptoms, whereas others might experience progressive deterioration in cardiac function that results in congestive heart failure, thromboembolism, arrhythmias, and sudden cardiac death.^{1–4} Therefore, early diagnosis and appropriate management are crucial.

The ability to detect LVNC in the fetus has been rarely described in this population. Although distinct criteria have been established for diagnosing LVNC after birth, those for fetal LVNC diagnosis remain unidentified.⁵ A previous study reported that continual morbidity and mortality rates occur in fetal cases of LVNC, even if treated with appropriate care perinatally and during childhood.^{6,7} Currently, there are no published data available on the long-term outcomes of fetuses diagnosed with LVNC.

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We conducted nationwide retrospective surveys of fetuses with cardiomyopathies (CMs) in Japan January 2010 to December 2016, by which we aimed to elucidate the clinical features, diagnosis, and prognosis of fetal LVNC.

Methods

Subjects

We conducted a multicenter, retrospective, observational study by inviting 131 hospitals with a fetal or pediatric cardiology department in Japan to participate in a survey of fetal patients with CMs from. After agreeing to participate, we sent a detailed questionnaire and DVD to 20 hospitals to obtain fetal and postnatal clinical and echocardiographic data. The questionnaire elicited maternal, fetal, and postnatal information, such as maternal and

Received November 6, 2020; revised manuscript received May 30, 2021; accepted June 15, 2021; J-STAGE Advance Publication released online August 3, 2021 Time for primary review: 16 days

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ISSN-1346-9843

family histories; diagnosis and prognosis; echocardiographic data in the fetal and postnatal periods; treatment after birth. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki 1975 and was approved by the Research Ethics Committee of the University of Toyama (approval no. R2016020), Toyama, Japan.

Measurements and Definitions

The LVNC diagnosis was based on the characteristic two-layered myocardium with a noncompacted to compacted (N/C) ratio >2.0 at end-diastole, and the observed disease process in >1 ventricular wall segment.^{7,8} Dilated cardiomyopathy (DCM) is characterized by cardiac dysfunction and ventricular enlargement. For a fetus, cardiac dysfunction was defined as left ventricular fraction shortening (LVFS) $<28\%$ and ventricular enlargement was defined as cardiothoracic area ratio (CTAR) $\geq 35\%$ unrelated to structural heart disease. Cardiomyopathy cases associated with positive anti-SS-A AV block and maternal diabetes were excluded. Hypertrophic cardiomyopathy (HCM) is clinically defined as obvious ventricular hypertrophy and a diastolic ventricular wall thickness >2.0 z-scores. The z-scores of the interventricular septum (IVS) and posterior wall (PW) were measured at end-diastole.⁹ We defined all the described cardiomyopathies in the prenatal and postnatal periods, and enrolled the patients who satisfied this definition. Hydrops fetalis is a condition characterized by abnormal accumulation of fluids in ≥ 2 compartments of the fetus such as skin edema, pleural effusion, and pericardial effusion. We used the cardiovascular profile score (CVPS) to assess the severity of fetal heart failure.¹⁰ The score includes 5 echocardiographic variables, and a score of 10 points indicates normal cardiac function (Supplementary Table 1). Two independent reviewers (S.W.O., K.H.), blinded to each other's measurements, analyzed the echocardiographic data. Intra- and interobserver variability were evaluated by repeating the analysis 8 weeks later by the same observer and a second investigator.

Endpoints

The primary endpoints were death or heart transplantation (HT), and the secondary endpoint was prenatal diagnosis of LVNC.

Statistical Analysis

Distributed data are summarized as means and standard deviations, whereas nonparametric data are presented as medians and interquartile range. χ^2 or Fisher's exact test was used for comparing the distributions of variables according to CM type, Tukey-Kramer method for numeric variables, and paired t-test for overtime variables. Cox's proportional-hazards model was used to assess risk factors for death. All the variables were first compared using separate univariate models, then a multivariate model. Receiver operating characteristic (ROC) curve analysis was conducted to determine the optimal cutoff levels of the number of derivations obtained from demographic and echocardiographic data to predict LVNC. Survival curves were plotted using Kaplan-Meier survival estimates; distributions of time to event outcomes according to CM type were compared using the log-rank test. We defined as zero month from the date of fertilization at event-free survival curve. Statistical significance was set at $P < 0.05$. Statistical calculations were performed using JMP Pro 14.2.0.

Results

Clinical Features

We collected data of 47 fetuses with CM. We excluded 9 fetuses from the study because of other than CM, arrhythmogenic cardiomyopathy, and endocardial fibroelastosis (Figure 1). Accordingly, 38 fetuses were enrolled in the study: 16 fetuses with LVNC, 15 with DCM, and 7 with HCM. They were diagnosed in the postnatal period. The demographic characteristics of the patients at first visit and outcomes are listed in Table 1 and Supplementary Table 2. Follow-up ranged from 0 days to 64 months (median, 10.5

Table 1. Baseline Clinical and Echocardiographic Characteristics of the Fetuses With Cardiomyopathy

	Total (n=38)	LVNC (n=16)	DCM (n=15)	HCM (n=7)	P value
Maternal age at diagnosis (years)	32.0 (22–41)	33.5 (27–41)	30.5 (22–40)	28.0 (26–37)	0.091
GA at diagnosis (weeks)	30 (18–39)	29 (24–36)	28 (22–38)	34 (18–39)	0.569
Sex (male)	22 (57.8%)	8 (50.0%)	10 (83.3%)	4 (80.0%)	0.148
Diagnosis opportunity					
Fetal heart screening	22 (57.8%)	10 (62.5%)	8 (53.3%)	4 (57.1%)	0.874
Hydrops fetalis	7 (18.4%)	2 (12.5%)	4 (26.6%)	1 (14.2%)	0.767
Family history of CM	10 (26.3%)	8 (50.0%)	2 (13.3%)	0 (0%)	0.020
Fetal complications	16 (42.1%)	6 (37.5%)	7 (46.6%)	3 (42.8%)	0.909
Hydrops fetalis	17 (44.7%)	4 (25.0%)	8 (53.3%)	5 (71.4%)	0.082
Congenital heart disease	12 (31.5%)	9 (56.3%)	2 (13.3%)	1 (14.3%)	0.024
Arrhythmia	4 (10.5%)	3 (18.5%)	0 (0%)	1 (14.2%)	0.218
Echocardiography					
Heart rate (beats/min)	140.4±10.6	141.1±9.7	136.6±10.8	150.0±8.8	0.168
CTAR (%)	39.5±7.3	40.1±6.0	39.2±6.5	39.0±11.9	0.927
CVPS	7.3±1.7	8.0±1.6	6.7±1.7	7.0±1.0	0.207
Mitral regurgitation	16 (42.1%)	2 (12.5%)	12 (85.7%)	2 (33.3%)	0.0001
Tricuspid regurgitation	22 (57.8%)	9 (56.3%)	10 (71.4%)	3 (50.0%)	0.660
LVFS (%)	22.1±9.2	24.8±11.5	18.2±5.6	26.5±9.1	0.339
Concordance between pre- and postnatal diagnoses	23 (60.5%)	9 (56.3%)	11 (73.3%)	3 (42.9%)	0.386
Death/HT	16 (42.1%)	4 (25.0%)	11 (73.3%)	1 (14.3%)	0.004
Intrauterine death	3 (7.9%)	1 (6.3%)	2 (13.3%)	0 (0%)	0.525

Values are n (%), mean±SD, or median (interquartile range). CM, cardiomyopathy; CTAR, cardiothoracic area ratio; CVPS, cardiovascular profile score; DCM, dilated cardiomyopathy; GA, gestational age; HCM, hypertrophic cardiomyopathy; LVFS, left ventricular fraction shortening; LVNC, left ventricular noncompaction.

Table 2. Clinical and Echocardiographic Characteristics at Birth

	Total (n=35)	LVNC (n=15)	DCM (n=13)	HCM (n=7)	P value
Transvaginal delivery	16 (42.1%)	7 (46.7%)	6 (46.2%)	3 (50.0%)	1.000
GA at birth (weeks)	37 (30–40)	37 (30–40)	36 (32–40)	37 (34–39)	0.739
Birth weight (g)	2,808±543	2,782±584	2,694±435	3,102±616	0.323
Birth height (cm)	47.2±2.9	47.1±3.0	42.2±2.5	49.7±2.4	0.932
Apgar score (1 min)	6±2.7	6.9±1.6	5.5±3.5	4.6±2.5	0.135
Apgar score (5 min)	7.2±2.5	7.8±1.9	6.6±3.4	7.1±0.7	0.474
Extracardiac involvement	5 (14.2%)	1 (6.6%)	1 (7.6%)	3 (42.8%)	0.181
Arrhythmia	6 (17.1%)	4 (26.6%)	1 (7.0%)	1 (14.0%)	0.824
Chest X-ray					
CTR	0.62±0.07	0.62±0.06	0.64±0.1	0.62±0.06	0.710
Pulmonary congestion	12 (34.2%)	4 (28.6%)	4 (44.4%)	4 (80.0%)	0.156
Echocardiography					
LVFS (%)	23.5±14.4	23.7±9.5	13.1±8.9	43.4±17.8	0.027
MR (>moderate)	8 (22.8%)	1 (6.6%)	6 (66.6%)	1 (16.6%)	0.005
IVS z-score	0.23±1.7	−0.1±0.4	−0.5±0.6	2.4±0.7	0.012
LVPW z-score	1.9±2.0	1.5±0.5	1.9±0.8	3.0±1.0	0.432
Treatment (subjects, %)	24 (26, 92.3%)	12 (13, 92.3%)	7 (8, 87.5%)	5 (5, 100%)	0.565
Diuretics	21 (87.5%)	12 (100%)	6 (85.7%)	3 (60.0%)	0.275
Catecholamine	20 (83.3%)	11 (91.6%)	6 (85.7%)	3 (60.0%)	0.457
Ventilator support	18 (75.0%)	9 (75.0%)	5 (71.4%)	4 (80.0%)	0.582
β-blocker	18 (75.0%)	10 (83.3%)	4 (57.1%)	4 (80.0%)	0.383
PDE3 inhibitor	15 (62.5%)	9 (75.0%)	5 (71.4%)	1 (20.0%)	0.197
ACE inhibitor/ARB	14 (58.3%)	9 (75.0%)	4 (57.1%)	1 (20.0%)	0.196
Antiplatelet/anticoagulant drug	8 (33.3%)	6 (50.0%)	1 (14.2%)	1 (20.0%)	0.355
PMI	2 (0.08%)	2 (16.6%)	0 (0%)	0 (0%)	0.601

Values are n (%), mean±SD, or median (interquartile range). ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; CTR, cardiothoracic ratio; HT, heart transplantation; IVS, interventricular septum; LVPW, left ventricular posterior wall; MR, mitral regurgitation; PDE, phosphodiesterase; PMI, pacemaker implantation. Other abbreviations as in Table 1.

Figure 2. Serial echocardiographic changes in the N/C ratios through the prenatal to postnatal period. **(A)** Serial changes in the N/C ratio at first prenatal visit (median 30 weeks of gestation (18–39weeks)), at last prenatal visit (median 36 weeks of gestation (27–39weeks)), and postnatal (birth) for patients with LVNC diagnosed after birth in the lateral wall (lefthand side) and apex (righthand side). **(B)** Serial changes in the N/C ratio at the lateral wall from the fetal first visit (lefthand side) to after birth (righthand side) among the 3 groups of cardiomyopathies. **(C)** Serial changes in N/C ratio at the apex from the fetal first visit (lefthand side) to after birth (righthand side) among the 3 groups of cardiomyopathies. DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LVNC, left ventricular noncompaction; N/C, noncompacted-to-compacted.

months). The median gestational age at diagnosis was 30 weeks (18–39 weeks). Fetal cardiac screening was the most effective examination for detecting and diagnosing CM in the fetuses (57.8%). Fetuses with LVNC had a significantly higher positive family history of CM than those with DCM and HCM ($P=0.020$). Fetal complications, such as positive nuchal translucency and intrauterine growth restriction, were observed in 16 fetuses (42.1%). The incidence of developing congenital heart disease (CHD) was significantly higher in fetuses with LVNC (9, 56.3%) than in fetuses with DCM and HCM ($P=0.024$).

Clinical Features After Birth

Almost all infants were born at term (full-term birth); however, half were delivered by cesarean section (Table 2). Findings of extra cardiac involvement were most frequently observed in patients with HCM (42.8%), whereas patients

with LVNC had the highest incidence of arrhythmias (26.6%). A total of 24 patients (92.3%) with CM received treatment, including angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, β -blockers, catecholamines, phosphodiesterase III inhibitors, diuretics, antiplatelets, anticoagulants, ventilator support, and pacemaker implantation. No significant differences were observed between patients with CM for each type of treatment. However, compared with the patients with DCM and HCM, patients with LVNC required multiple treatments.

Echocardiographic Findings

The echocardiographic characteristics at first visit are shown in Table 1. Mitral regurgitation (MR) of any grade was frequently observed in the fetuses with DCM compared with those with LVNC and HCM ($P=0.0001$). Echocardiographic findings after birth are given in Table 2.

Figure 3. Flow chart of diagnosis of patients with LVNC before and after birth with their outcomes, showing discrepancies between prenatal and postnatal diagnosis and prognosis. HCM, hypertrophic cardiomyopathy; LVNC, left ventricular noncompaction.

Table 3. Univariate and Multivariate Cox Proportional-Hazards Regression Analysis for the Independent Predictors of HT or Death						
	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	P value	Odds ratio	95% CI	P value
Sex (male)	12.0	1.30–110.52	0.0072			
DCM diagnosis at birth	16.5	3.09–88.03	0.0002	18.7	1.40–248.39	0.0265
CVPS <7	21.0	1.94–227.20	0.0026	26.9	1.46–495.26	0.0266
Prenatal MR	7.5	1.60–34.95	0.0065			
Postnatal MR (>moderate)	18.9	2.54–141.92	0.0015			
Pulmonary congestion at birth	7.0	1.08–45.15	0.0283			

CI, confidence interval. Other abbreviations as in Tables 1,2.

Reduced LVFS was noted in patients with DCM (13.1±8.9%, P=0.027). Moderate and severe MR was more frequently detected in patients with DCM than in patients with LVNC and HCM (P=0.005). The IVS z-score was significantly higher in patients with HCM than in patients with LVNC and DCM (P=0.012).

Serial Echocardiographic Variables

Prominent trabeculations were mostly observed in the lateral LV, posterior LV, and apex of the LV in patients with LVNC compared with those with DCM and HCM between the fetal and neonatal periods (Figure 2, Supplementary Figure 1). The N/C ratio was significantly higher in patients with LVNC than in patients with DCM and HCM at first visit (lateral LV: 1.6±0.1, 0.4±0.2, and 0.5±0.4, P=0.006; LV apex: 2.0±0.1, 0.6±0.2, and 1.0±0.4, P=0.003, respectively). Of note, the N/C ratio at the apex and lateral wall increased time-dependently from the fetal period to birth. After birth, the N/C ratio was significantly higher in patients with LVNC than in patients with DCM and HCM (lateral LV: 2.8±0.2, 0.6±0.3, and 0.6±0.5, P=0.001; LV apex: 3.2±0.2, 0.7±0.4, and 0.5±0.6, P=0.001, respectively). Thus, the N/C ratios after birth in the LVNC group were higher than 2.0 for both the lateral LV and LV apex, whereas the N/C ratios in LVNC during the fetal period were slightly lower than 2.0.

Concordance Between Prenatal and Postnatal Diagnoses

We reviewed the prenatal diagnoses retrospectively and

analyzed the concordance between the prenatal and postnatal diagnoses. The concordance rate for CM was 60.5%; LVNC 56.3%, DCM 73.3%; HCM 42.9% (Table 1, Figure 3, Supplementary Figure 2). Of 16 patients with LVNC, 9 (56.3%) were diagnosed at the first visit; there was 1 intra-uterine death and 2 other patients died, which was a higher mortality rate than in patients with HCM and a lower concordance rate than in patients with DCM.

Prognosis of CM and Risk Factors for Death and LVNC

During the period of the study, 16 patients died or underwent HT: 4 with LVNC, 11 DCM, 1 HCM (Table 1). Of these patients, 3 died during the fetal period: 1 with LVNC and 2 with DCM. No significant differences were observed in terms of other clinical parameters among the fetuses with CM. The multivariate proportional-hazards model, including fetal echocardiographic parameters, showed that final DCM diagnosis at birth and CVPS score <7 were independent risk factors for death or HT in all patients with CM (odds ratio (OR): 18.7, 95% confidence interval (CI): 1.4–248.39, P=0.026; OR: 26.9, 95% CI: 1.46–495.26, P=0.026, respectively) (Table 3, Figure 4). In addition, CM patients with MR at the final visit had significantly higher mortality rates than those without MR during the prenatal period (P=0.0185) (Figure 4).

The multivariate proportional hazards model showed that N/C ratio ≥1.6 at the apex at the first visit in the fetus was a significant predictor of LVNC (OR: 47.8, 95% CI: 2.39–956.39, P=0.0113) (Table 4). The ROC curve was

Figure 4. Event-free survival in patients with cardiomyopathies. Event-free survival to endpoints of death or HT in patients with cardiomyopathies according to type (A), CVPS at first prenatal visit (B), and MR at last prenatal visit (C). CVPS, cardiovascular profile score; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LVNC, left ventricular noncompaction; MR, mitral regurgitation.

Table 4. Univariate and Multivariate Cox Proportional-Hazards Regression Analysis for the Independent Predictors of Fetal LVNC

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	P value	Odds ratio	95% CI	P value
Family history of CM	10.0	1.73–57.7	0.0100			
Congenital heart disease	8.14	1.69–39.05	0.0088			
N/C ratio ≥1.7 at the lateral wall	12.8	1.31–125.77	0.0282			
N/C ratio ≥1.6 at the apex	69.9	5.55–882.19	0.0010	47.8	2.39–956.39	0.0113

N/C, noncompacted-to-compacted. Other abbreviations as in Tables 1,3.

screened and the area under the curve of the N/C ratio at the apex was 0.892. The sensitivity and specificity were 87.5% and 90.9%, respectively for the diagnosis of fetal LVNC (Supplementary Figure 3).

Discussion

In this study, we demonstrate the etiology of fetal CM from a large cohort in Japan. Moreover, this is the first longitudinal study of the clinical and echocardiographic features during the perinatal period in patients with

LVNC. Our study shows that reaching a definitive diagnosis during the fetal period is challenging, and highlights the need for new diagnostic criteria for LVNC because the prognosis varies according to the fetal onset of CM types.

According to the annual survey of the Japanese Society of Pediatric Cardiology and Cardiac Surgery (2005–2014), the occurrence of LVNC, DCM, and HCM in the whole pediatric populations was 28.7, 43.1, and 35.8 persons per year, respectively.¹¹ Therefore, the occurrence of LVNC, DCM, and HCM in patients under 1 year of age was 12.6, 19.5, and 10.0 persons per year, respectively. In this study,

over 7 years, we collected the data of 38 patients from 20 hospitals out of 131 relevant hospitals in Japan. Thus, taking into account that the collection rate was 15.3%, the estimated occurrence of LVNC, DCM, and HCM in fetuses in this study was 14.9, 14.0, and 6.5 fetuses per year, respectively. These data are compatible with data reported in the annual Japanese survey and showed that the populations of fetal onset of LVNC, DCM, and HCM with respect to the whole pediatric CM cohort were 51.9%, 32.4%, and 18.1%, respectively. The annual number of births was approximately 1,000,000 in Japan (2014), indicating that the incidence of babies with LVNC, DCM, and HCM was 1.49, 1.40, and 0.65 per 100,000 babies, respectively.

Previous studies adopted the diagnostic criteria of LVNC in fetal patients that are used for children and adult patients with LVNC.⁷ However, our results showed that when these criteria are applied, there can be failure to diagnose some patients with LVNC in utero because the prominent trabeculations gradually appear in the later stage of pregnancy. It has been reported that CM may develop later in pregnancy even if earlier fetal echocardiography shows normal ventricular size and function.¹² Besides, the N/C ratio of the myocardium in the normal fetus is much higher than that in children and adults,¹³ indicating that compaction of the fetal LV myocardium has not completely developed even in the late gestational stage and that compaction of the fetal LV develops gradually.¹⁴ Thus, our results showed that it is difficult to detect LVNC early in utero and highlighted the need for specific diagnostic criteria of fetal LVNC.

At 5–8 weeks of gestation, the ventricular myocardium gradually compacts. The densification of the fetal LV myocardium occurs gradually from the base to the apex and from the anterior to the lateral, posterior, and inferior walls.¹⁵ By the 12th week of embryonic development, the compaction process is completed.¹⁶ Failed compaction of embryonic trabeculations might lead to LVNC, whereby an excessive number of trabeculations linger in the ventricular lumen.¹⁷ However, our results did not support the hypothesis that arrest of the compaction of the LV wall leads to LVNC, because there were greater thickness of trabeculations in the late gestational stage than in the mid-gestational stage. A recent study reported that noncompaction results from abnormal growth of the compact wall. Alternatively, another study suggested that the excessive trabeculations in noncompaction do not have an embryonic identity and failed compaction probably does not result in noncompaction.¹⁸ Pressure overload of the LV is another possible mechanism. Cardiac output is reported to be 210 mL/min and 1,900 mL/min at 20 to 38 week gestation, respectively.¹⁹ From 30- to 38-week gestation, cardiac output increases two-fold. In adult patients, acquired LVNC occurs in athletes and patients with sickle cell anemia, pregnancy, myopathies, and chronic renal failure.^{20,21} During LV pressure overload,²² a change in LV morphology and a decrease in LV mass may occur, resulting in the manifestation of prominent trabeculations in the LV. As well as these previous observations, additional stress to the myocardium may trigger a deterioration of systolic function, resulting in prominent trabeculations in the LV during the fetal period, because LVNC is frequently associated with systolic dysfunction. All in all, our longitudinal observations from echocardiography in the fetus suggest a new hypothesis that physiological mechanical stress to an impaired LV myocardium, even during the fetal period, plays a role in the development of LVNC rather than the

current hypothesis of developmental escape for maturity.

Our results revealed that high mortality rates and severe symptoms are associated with fetal LVNC. Fetuses with LVNC usually have enlarged and poorly functioning ventricles.^{7,23} A few studies only reported the successful outcomes of diagnosing LVNC in utero. A recent review of 106 published cases showed that only 46 patients with prenatally diagnosed LVNC were alive after birth,²³ and the remaining 60 patients died due to termination of pregnancy or intrauterine death or during the first few weeks of postnatal life. Our results showed that CHD involvement was noted in 9 patients (56.3%). LVNC is often associated with various CHDs, many of which have serious anatomic and physiologic consequences leading to eventual cardiac failure and neonatal death, so even in isolation it is a significant predictor of severe cardiac failure.^{7,24} Therefore, poor cardiac function during the fetal period and the complications of CHD may strongly affect the prognosis of fetal onset of LVNC.

Study Limitations

This was a retrospective study and most of the patients were referrals from outside facilities; therefore, there was no long-term follow-up of the patients. Moreover, due to the retrospective nature of the study, we only selected patients with LVNC diagnosed in utero. The present study was conducted over approximately 7 years, and, during this time, therapies have been developed that may have altered patient outcomes.

Conclusions

We demonstrated the etiology of fetal CM based on a nationwide survey conducted in Japan. Our results revealed that diagnosing LVNC in fetal patients is challenging despite the greater caution of LVNC with poor prognosis. Early detection of LVNC will result in early intervention and treatment to delay the progression of heart failure and improve the quality of life. To better understand and manage fetal CM, novel diagnostic criteria of LVNC in a fetus should be established. Further large-scale cohort studies with genetic testing and high-resolution modalities, such as magnetic resonance imaging, are warranted.

Acknowledgments

The authors acknowledge the expert technical assistance of Hitoshi Moriuchi, Haruna Hirai and Eriko Masuda for.

Funding

This study was supported financially by JSPS KAKENHI Grant number 16K10063.

Disclosure

The authors declare no conflicts of interest.

IRB Information

The study protocols were approved by the Research Ethics Committee of the University of Toyama (approval no. R2016020).

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Supplementary Files

Please find supplementary file(s);
<http://dx.doi.org/10.1253/circj.CJ-20-1148>