Table 1. Patient Features vs. Presence of Aortic Dilatation or Dissection

	Group D (n=11)	Group ND (n=17)	P value
Maternal age (years)†	29.5±3.5	30.1±4.0	NS
Height (cm)†	167.3±4.5	165.3±4.2	NS
Weight (kg)†	65.3±4.5	64.5±3.9	NS
Nulli/Multiparous‡	8/3	12/5	NS
Gestation (weeks)†	36.2±3.2	37.0±2.8	NS
Birth weight (g)†	2747±705	2769±599	NS
Delivery mode‡			<0.005
Vaginal delivery	4	14	
Cesarean section	7	3	
BMI†	24.2±1.5	24.1±1.8	NS
DM‡	2	3	NS
Hypertension‡	2	3	NS
Smoking‡	2	3	NS

Data given as n or mean±SD. †Student's t-test; ‡chi-square test and Fisher's exact test. P<0.05, significant difference. D, aortic dilatation or dissection; ND, no aortic dilatation nor dissection; BMI, body mass index; DM, diabetes mellitus.

Table 2. Diagnostic Categories for Marfan Syndrome (Ghent Criteria [9])

Category	Group D (n=10)		Group ND (n=12)	
	Major	Minor	Major	Minor
Skeletal	10	3	11	2
Ocular	2*	1	8*	1
Cardiovascular	10*	3	7*	5
Pulmonary	–	3	–	2
Skin	–	0	–	1
Dura	2	–	5	–

Data were analyzed using chi-square test and Fisher's exact test. *P<0.05.
Abbreviations see in Table 1.

eter ≥4.0 cm[7–10,12,13] and a steady increase in the aortic root dimension during pregnancy.[9,10,14] Meijboom et al reported that pregnancy in women with Marfan syndrome seems to be relatively safe up to an aortic root diameter of 45 mm.[15] Most previous reports on Marfan syndrome in pregnancy, however, have been from North America or Europe, and people in these areas have relatively large physiques, and patient physique was not standardized. Because normal aortic dimensions vary with age and body size,[16] the same aortic dimension represents a proportionally greater diameter in smaller individuals, and proper interpretation of the aortic dimension requires that age and body size are accounted for. Therefore the absolute aortic size cannot be directly used to evaluate risk in patients with a small physique,[17] such as Japanese women.

The risk factors for aortic complications in pregnant patients affected with Marfan syndrome have not been examined relative to body surface area. Therefore, to improve patient management, we studied 28 consecutive pregnant patients with Marfan syndrome in 1 institution to determine the factors that influence maternal aortic complications.

Methods

Patients

We retrospectively analyzed 28 consecutive pregnant patients with Marfan syndrome who were managed at the National Cerebral and Cardiovascular Center from 1991 to 2007. Diagnosis of Marfan syndrome was made based on the original Ghent criteria (1996).[18] Cases before 1996 were confirmed to fulfill these criteria. The initial assessment included an evaluation of personal history and detailed family history, and a clinical examination including ophthalmological tests and a transthoracic echocardiogram.[3] X-ray was used to detect protrusion acetabulae, and lumbar magnetic resonance imaging (MRI) was performed to detect dural ectasia.

We divided the patients into 2 groups: those with aortic dilatation or dissection (group D, n=11) during pregnancy or within 1 year after delivery and those without aortic dilatation or dissection (group ND, n=17). Aortic dilatation was defined as a diameter >60 mm at any part of the aorta.

Measurement of Aortic Diameter and Indication for Surgery

Measurement of the sinus of Valsalva was made on echocardiography in 2-D parasternal long-axis views at end-diastole using the leading edge to leading edge method.[16,19] MRI and computed tomography were not routinely used. The Japanese Circulation Society recommends an operation for patients with a sinus of Valsalva >5 cm (class IIa, level C) in all cases of Marfan syndrome.[20] Some surgeons also recommend an operation for patients with a sinus of Valsalva >4.5 cm.[21] At the National Cerebral and Cardiovascular Center, surgical intervention is indicated according to the aforementioned criteria and for patients with a family history of dissection or sudden death. In general, surgical intervention is indicated for a sinus of Valsalva >4.0 cm or in a case of steady aortic growth.[22,23] During pregnancy, surgical intervention is indicated if there is steady aortic growth or massive dissection. To standardize the measurement based on body size, we expressed the size of the sinus of Valsalva using the aortic size index (ASI), which is calculated as: ASI=aortic diameter (mm)/body surface area (m^2).[17]

Management During Pregnancy

Echocardiographic follow-up including aortic diameter measurement and Holter electrocardiogram was performed at least once in each trimester during pregnancy and within 4 weeks after delivery. When surgical intervention was indicated, the operation was performed after cesarean section in the case of a mature fetus. When the fetus was too immature to live independently, the operation was performed with the fetus in the uterus.

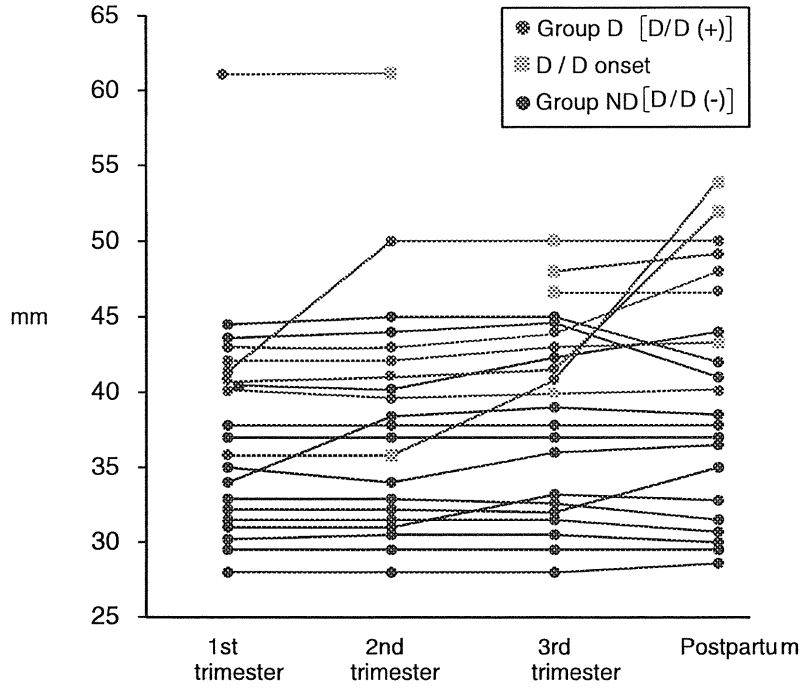

Figure 1. Diameters of the sinus of Valsalva. D/D, aortic dilatation or dissection. Red, presence of aortic dilatation or dissection; blue, absence of aortic dilatation or dissection (group D and group ND, respectively). Pink, cardiac event. In the 1st trimester a larger sinus of Valsalva was found in group D compared to group ND (41.5±2.4mm vs. 34.8±1.3mm P<0.05; Student's t-test). The sinus of Valsalva was ≥40mm in 6/7 patients in group D and 3/14 in group ND (P<0.05; chi-square test and Fisher's exact test).

Table 3. Echocardiographic Findings vs. Presence of Aortic Dilatation or Dissection

Item	Group D (n=11)	Group ND (n=17)	P value
Sinus of Valsalva (mm) in first trimester†	44.1±10.2	34.8±5.5	<0.005
Growth of aorta (mm/month)‡	0.41 (0.23–0.66)	0.05 (–0.13 to 0.22)	<0.005
Aortic valve regurgitation§			
None-Mild	5	15	<0.05
Moderate-Severe	6	2	
Mitral valve prolapse§	6	3	<0.05
LVDd†	45.8±7.1	44.8±6.8	NS
LVDs†	31.1±4.7	30.1±4.6	NS
%FS†	36.5±5.6	37.5±4.6	NS
RA cavity enlarged§	2	3	NS
RV cavity enlarged§	2	2	NS
PA dilatation (≥20mm)§	3	2	NS

Data given as mean±SD, n, or median (interquartile range).
†Student's t-test; ‡Wilcoxon test; §chi-square test and Fisher's exact test. P<0.05, significant difference.
LVDd, left ventricle end-diastolic dimension; LVDs, left ventricle end-systolic dimension; FS, fractional shortening; RA, right atrium; RV, right ventricle; PA, pulmonary artery. Other abbreviations see in Table 1.

Data Collection

Data were collected on family history (sudden death, aortic dilatation or dissection), maternal age, body height, body weight, parity, presence or absence of hypertension, diabetes mellitus, change in the diameter of the sinus of Valsalva during and after pregnancy, right and left ventricular function, aortic valve regurgitation, mitral valve prolapse, delivery mode (Cesarean section or vaginal delivery), time of delivery (gestational weeks), and birth weight.

Statistical Analysis

For continuous variables, Student's t-test was used for analysis of normally distributed data and the Wilcoxon test was used for data that were not normally distributed. A chi-squared test and a Fisher's exact test were used for comparing categorical variables between the 2 groups. All statistical analyses were performed using JMP 7 (SAS Institute, Cary, NC, USA). P<0.05 was considered statistically significant.

Results

Aortic Dilatation or Dissection Group

Eleven patients had aortic dilatation or dissection associated with pregnancy (in 7 this occurred during pregnancy and in 4 it occurred within 1 year after pregnancy). Two of the 7 antepartum cases involved aortic dilatation >60mm (maximum diameter of the aorta) in the 2nd trimester at 16 and 19 weeks of gestation, respectively. One patient underwent hemiarch

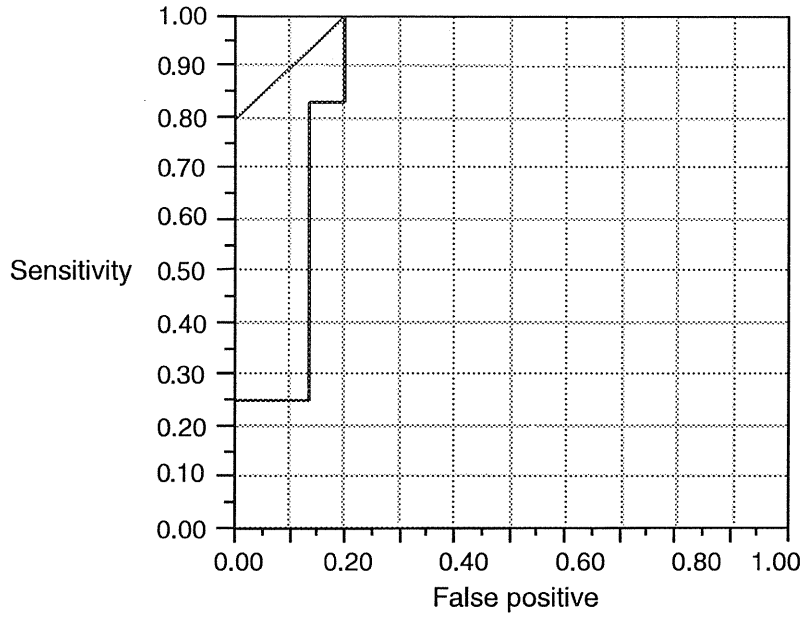

Figure 2. Receiver operating characteristic curve for the risk of dilatation or dissection based on the size of the sinus of Valsalva.

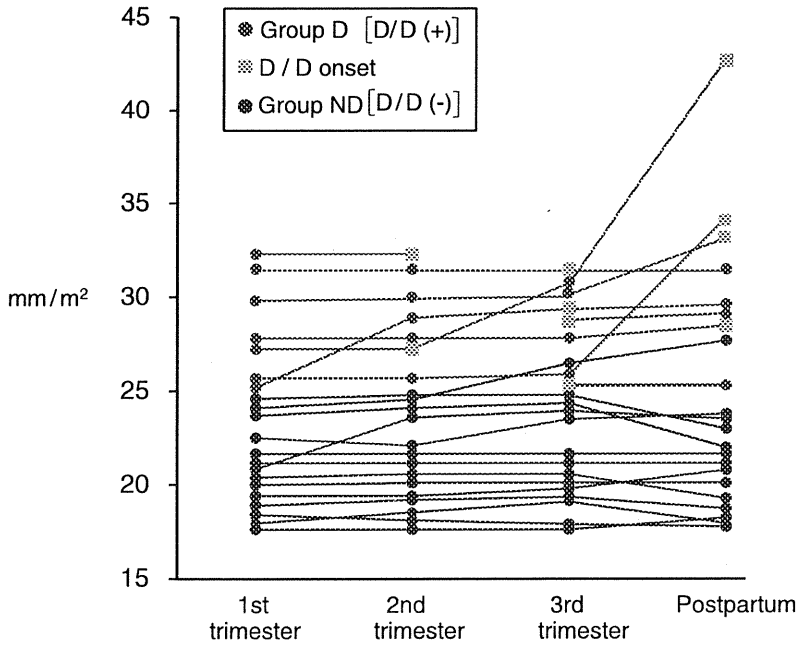

Figure 3. Sinus of Valsalva relative to body surface area (size of the sinus of Valsalva/body surface area: mm/m²). D/D, aortic dilatation or dissection. Red, presence of aortic dilatation or dissection; blue, absence of aortic dilatation or dissection (group D and group ND, respectively). In the 1st trimester the normalized size of the sinus of Valsalva was ≥25mm/m² in 7/7 patients in group D and 0/14 in group ND (P<0.0001; chi-square test and Fisher's exact test).

replacement and the other underwent a David operation under cardiopulmonary bypass with the fetus in the uterus. The other 5 dissections during pregnancy occurred at 29, 33, 34, 35 and 39 weeks of gestation. Of these 5 patients, 3 underwent Bentall operations following cesarean section and 2 received conservative therapy after cesarean section. Dissection in the 4 postpartum cases occurred at 4 days, 8 months, 18 months, and 11 months after delivery, respectively. Of the 11 dilatation or dissection cases, 8 occurred in the ascending aorta, 1 in the descending aorta, and 2 in both locations.

Demographic Patient Data

The maternal age, week of delivery, and birth weight did not differ between the D and ND groups (Table 1). The incidence of cesarean section was higher in group D than in group ND (7/11, 63.6% vs. 3/17, 17.6%, P<0.05). This was attributed to performance of cesarean section due to occurrence of dilatation or dissection of the aorta during pregnancy. The number of patients meeting each diagnostic category for Marfan syndrome (Ghent criteria, 1996)[18] is given in Table 2. In group D, fewer patients met the major ocular criteria (2/10, 20% vs.

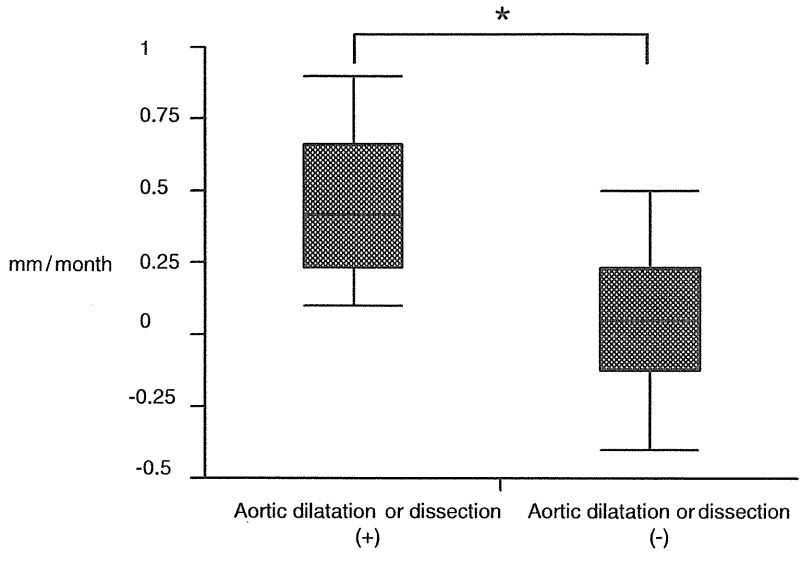

Figure 4. Rate of growth of the sinus of Valsalva. Significantly faster growth of the sinus of Valsalva was observed in group D (red) than in group ND (blue). The middle bar indicates the 50th percentile; box edges are the 25th and 75th percentiles; and outer bars are the 10th and 90th percentiles. Data were analyzed using Wilcoxon test. *P<0.05.

8/12, 67%, P<0.05) and more patients met the major cardiovascular criteria (10/10, 100% vs. 7/12, 58%, P<0.05). Gene analysis was performed in 11 of the 28 cases (40%) and a fibrillin-1 mutation was found more commonly in group D, although the difference was not significant (4/4, 100% vs. 4/7, 57%, P=0.06). A family history of sudden death or aortic dissection was more frequent in group D (7/11, 64% vs. 4/17, 24%, P<0.05).

Echocardiographic Patient Data

The sinus of Valsalva in the 1st trimester of pregnancy was significantly larger in group D than in group ND (mean [range]: 44.1 mm [36–61 mm] vs. 34.8 mm [28–45 mm], P<0.005; Figure 1; Table 3) and a sinus of Valsalva ≥40 mm in the 1st trimester was more frequent in group D (6/7, 86% vs. 3/14, 21%, P<0.05; Figure 1). On receiver operating characteristic (ROC) analysis of the relationship of the size of the sinus of Valsalva in the 1st trimester with aortic dilatation or dissection during pregnancy and after birth, the area under the curve (AUC) was 0.837 and the size of the sinus of the Valsalva that produced the best sensitivity (1–specificity) was 40 mm (Figure 2).

An ASI (diameter of the sinus of Valsalva/body surface area) ≥25 mm/m^2 was more frequent in group D than in group ND (7/7, 100% vs. 0/14, 0%; P<0.0001; Figure 3). On ROC analysis of the relationship of the ASI in the 1st trimester with aortic dilatation or dissection during pregnancy and after birth, the AUC was 0.985 and the size of the sinus of Valsalva that produced the best sensitivity (1–specificity) was 25 mm/m^2. In 1 case, aortic dissection occurred in a patient with a sinus of Valsalva of only 36 mm in the 1st trimester. Her ASI, however, was 27.3 mm/m^2 (36 mm/1.31 m^2), which was the 5th largest in the study. This indicates that normalizing the sinus of Valsalva measurement with respect to body surface area is more appropriate for prediction of aortic dilatation or dissection, compared to the absolute diameter. Significantly faster growth of the sinus of Valsalva was also observed in group D (median [interquartile range]: 0.41 mm/month [0.23–0.66 mm/month] vs. 0.05 mm/month [–0.13 to 0.22 mm/month]; P<0.05; Figure 4).

The sizes of the right and left ventricles did not differ between the 2 groups (Table 3). In the 1st trimester of pregnancy, patients in group D had more frequent moderate to severe aortic valve regurgitation (6/11, 55% vs. 2/17, 12%; P<0.05) and mitral valve regurgitation (6/11, 55% vs. 3/17, 18%; P<0.05). These effects were already present before conception and may be 1 of the causes of dilatation or dissection.

Discussion

This is the first study to investigate the risk factors for pregnancy-associated dilatation or dissection in Japanese patients with Marfan syndrome. The risk factors that differed significantly between groups D and ND were mostly consistent with those found in previous studies.[7–10,14] These factors included a large sinus of Valsalva, rapid growth of the sinus of Valsalva during pregnancy, moderate to severe aortic valve or mitral valve regurgitation, and a family history of sudden death or aortic dissection.

We found that a large sinus of Valsalva (≥40 mm) at the start of pregnancy was a risk factor for dilatation or dissection during pregnancy and after birth. The present result differs from the findings of the relatively large prospective study by Meijboom et al, in which it was concluded that pregnancy in women with Marfan syndrome seems to be relatively safe up to an aortic root diameter of 45 mm,[15] and from Canadian guidelines that recommend that women with an aortic root diameter beyond 44 mm should be strongly discouraged from becoming pregnant.[24] Taking into account that Japanese women have a generally smaller physique than European and North American women, we recommend that the cut-off for Japanese patients for advice regarding avoidance of pregnancy should be a sinus of Valsalva diameter ≥40 mm, rather than ≥45 mm. In a case report on a patient who developed a massive retrograde type B aortic dissection 7 days after normal spontaneous vaginal delivery, Gandhi et al described the patient as "petite" (body surface area, 1.69 m^2), but this is still larger than the average Japanese woman.[25]

We also suggest that normalizing the diameter of the sinus of Valsalva with regard to body surface area (diameter of the Valsalva/body surface area; mm/m^2) may be more appropriate

for detection of high-risk cases at the start of pregnancy. The relative aortic size was first used to predict complications in patients with thoracic aortic aneurysms.[17] We found that an ASI ≥25 mm/m² in the 1st trimester is associated with a high risk for aortic dilatation or dissection during pregnancy and after birth. The ASI is a novel measurement of relative aortic size that predicts rupture of aortic aneurysm,[17] and Davies et al found that the ASI was more important than absolute aortic size in predicting aortic complications, especially in smaller women such as those in the Japanese population.[17] We found that there was more rapid growth of the sinus of Valsalva in patients with Marfan syndrome with pregnancy-associated aortic dilatation or dissection, compared to those without these conditions. Therefore, even if the diameter of the sinus of the Valsalva is small, rapid growth carries a risk of aortic dissection or dilatation. The same phenomenon has been reported in non-pregnant cases of Marfan syndrome. Meijboom et al followed 108 women with Marfan syndrome and aortic root growth prospectively using serial echocardiograms, and found that the patients could be divided into 2 normally distributed groups based on aortic growth rates: 90% had slow growths and 10% had fast growth.[15] Significantly more dissections of the ascending aorta (25% vs. 4%, P<0.001) were observed in the fast growth group, and the average growth of the sinus of Valsalva in the fast group was 1.8 mm/year. The median growth in the present 5 cases of aortic dissection was as high as 4.1 mm/year. This large increase relative to that in the Meijboom et al study[15] is probably due to the maternal cardiovascular changes in pregnancy, including increased blood volume, heart rate, and stroke volume.[25] Furthermore, hormonally mediated histological changes also occur in the aorta, including a decrease in mucopolysaccharides and loss of elastic fibers in the aortic wall.[26–28] Care is therefore required in treating patients with a high growth rate of the sinus of Valsalva. The frequency and degree of aortic and mitral valve regurgitation were also higher in patients with aortic dilatation or dissection, and these valvular changes may have been the causes of dilatation or dissection.

An international expert panel established the revised Ghent criteria in 2010, which, first, focused more on cardiovascular manifestations, and in which aortic dilatation/dissection and ectopia lentis are the cardinal clinical features.[29] Second, in these revised criteria, a more prominent role is assigned to molecular genetic testing of FBN1 and other relevant genes in the diagnostic assessment. Third, some of the less specific manifestations of Marfan syndrome were either removed or made less influential in the diagnostic evaluation of patients. The new criteria also differentiate Marfan syndrome from Marfan-related syndromes such as Loeys-Dietz syndrome, Ehlers-Danlos syndrome, and familial thoracic aortic aneurysm syndrome, which are associated with a significantly greater risk of cardiovascular problems.[29–31] In the present study, patients with dilatation or dissection of the aorta were less likely to meet major ocular criteria, and more likely to meet the major cardiovascular criteria and had a more frequent family history of dilatation or dissection. These findings indicate that the new diagnostic criteria for Marfan syndrome facilitate identification of high-risk patients for pregnancy-associated dilatation or dissection more accurately.

Study Limitations

The disease severity of the present patients may have been higher than that of general Marfan syndrome patients because the National Cerebral and Cardiovascular Center is a referral center for cardiovascular diseases, and we also perform gene analysis.[32] Therefore, most Marfan syndrome patients are referred to our center due to cardiovascular complications and many have a family history of aortic complications. Also, because we investigated the clinical courses of Marfan syndrome patients associated with pregnancy in one institution, only 28 patients were included in the study. The small number of subjects prevented correction of the results for the effects of potential confounding factors such as hypertension, and we could not perform multifactorial analysis. The present study, however, has the advantage of clear definition of medical and surgical treatment and obstetric management. Measurements of the aorta, ventricle and atrium, and the degree of mitral and aortic valve regurgitation were also better defined in the present study compared with multi-center studies. In future research we plan to investigate a larger cohort of patients to clarify the risk factors for dilatation or dissection of the aorta in patients with Marfan syndrome during pregnancy.

Conclusion

An increased size of the sinus of Valsalva (≥40 mm) was found in Japanese patients with Marfan syndrome who experienced aortic dilatation or dissection during or after pregnancy. The ASI (size of the sinus of Valsalva/body surface area) is a better indicator of the risk for aortic dilatation or dissection during pregnancy and after birth, compared to the absolute size of the sinus of Valsalva. Until a molecular-based approach is available to identify patients at high cardiovascular risk, echocardiographic variables will remain as the most important prognostic factors. Prospective validation of the present proposed criteria is needed, but we suggest that the present strategy may be particularly useful for treatment of women with a small physique, who are common in the Japanese population.

Acknowledgments

We are indebted to the medical technologists at the National Cerebral and Cardiovascular Center for their important contributions to the study.

Disclosure

None of the authors have a conflict of interest to disclose.

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ORIGINAL ARTICLE
Pediatric Cardiology and Adult Congenital Heart Disease

Outcome of Pregnancy and Effects on the Right Heart in Women With Repaired Tetralogy of Fallot

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Background: Improved medical techniques have allowed most women with repaired tetralogy of Fallot (TOF) to reach childbearing age. The predictors of adverse events and the effects of pregnancy on cardiac function have not been clearly described in these patients.

Methods and Results: In the present study we retrospectively reviewed 40 deliveries in 25 patients with repaired TOF. There were 23 patients in New York Heart Association (NYHA) class I, and 2 in classes II–III before pregnancy. The mean age at delivery was 29.1 years and the mean gestational period was 37.8 weeks. Seven pregnancies (17.5%) in 7 patients were complicated with cardiac events such as a decline in NYHA class and arrhythmia. History of ablation and the baseline cardiothoracic ratio on chest radiography were predictors of adverse events. Peak plasma brain natriuretic peptide (BNP) level after the second trimester was higher in patients with cardiac events. Left ventricular size and contraction did not change from before to after pregnancy, but the right ventricle was enlarged at 6 months after delivery.

Conclusions: Many of the pregnancies in women with repaired TOF were successful. However, careful management is required for some patients and the BNP level may be a useful marker to identify these patients. Because the right heart tended to be enlarged in the late postpartum period, pregnancy may also affect the long-term prognosis of patients with repaired TOF. (*Circ J* 2012; **76:** 957–963)

Key Words: Arrhythmia; Congenital heart disease; Heart failure; Outcomes; Pregnancy

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease, and is characterized by a large ventricular septal defect (VSD), right ventricular outflow tract obstruction, right ventricular hypertrophy, and overriding of the aorta. Improvements in medical and surgical treatment have permitted most female patients with TOF to reach childbearing age after intracardiac repair. Several reports have shown relatively favorable pregnancy outcomes among such patients,[1–3] although with adverse maternal events associated with left ventricular dysfunction, severe pulmonary hypertension, and severe pulmonic regurgitation with right ventricular dysfunction.[1,4] However, few studies have analyzed the pregnancy-associated risks in these patients using physiological and radiological examinations, including evaluation of persistent cardiac changes after each pregnancy. Therefore, the aims of this study were (1) to characterize the risk factors for pregnancy-associated cardiac events, and (2) to evaluate the long-term effects of pregnancy on the heart in women with repaired TOF.

Methods

Patients

We retrospectively reviewed a series of 25 pregnant women with repaired TOF who delivered at the National Cerebral and Cardiovascular Center from 1987 to April 2010. Data were obtained from medical records. The 25 subjects had a total of 40 deliveries. Spontaneous or elective abortions were excluded from the study population. Baseline data were obtained for age, basic cardiac anatomy, history of prior surgery, cardiac events, medications, and smoking habit. New York Heart Association (NYHA) functional class, results from chest radiography, ECG, transthoracic echocardiography, and the plasma brain natriuretic peptide (BNP) level were reviewed from 1

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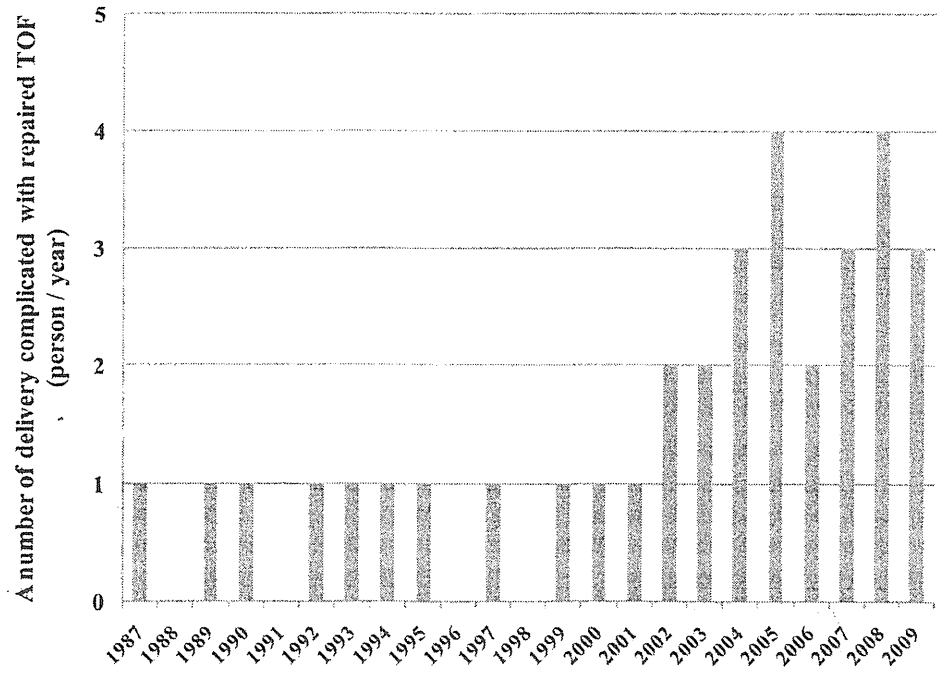

Figure 1. Annual number of deliveries complicated with repaired TOF at the National Cerebral and Cardiovascular Center. TOF, tetralogy of Fallot.

year before pregnancy to 1 year after delivery.

Outcomes

Cardiac events were defined as new onset or worsening of arrhythmia requiring treatment, heart failure (a decline in NYHA class, pulmonary congestion confirmed by chest radiography, requirement for diuretic therapy), endocarditis, or thromboembolic events during pregnancy to 1 month after delivery. Obstetric events were defined as pregnancy-induced hypertension (PIH: systolic blood pressure (BP) ≥140 mmHg or diastolic BP ≥90 mmHg after 20 weeks of gestation),[5] premature labor (labor before 37 weeks of gestation), and postpartum hemorrhage (blood loss in vaginal delivery ≥800 ml or in cesarean delivery (CS) ≥1,500 ml).[6] Offspring events were defined as small-for-gestational-age (SGA, birth weight <10th percentile), complication with congenital heart disease, and intrauterine or neonatal death (within 28 days). To analyze the risk factors for pregnancy-associated cardiac events, we compared the latest pregnancy between patients with and without cardiac events.

Physical Examinations

Results of chest radiography and ECG performed within 1 year before pregnancy to the first trimester (until 13 weeks of gestation) were used as baseline data. Cardiothoracic ratio (CTR) and QRS duration were measured. Patients with pacemaker rhythm were excluded from the assessment of QRS duration on echocardiography. The patients were routinely examined by transthoracic echocardiography by 2 skilled ultrasonographers who were in charge of obstetric patients and were blinded to the study. We obtained echocardiographic data on 4 occasions: (1) within 1 year before pregnancy to the first trimester, (2) in the second and third trimester (from 14 weeks of gestation to delivery), (3) after delivery to 1 month postpartum, and (4) from 6 months to 1 year after delivery. Patients who started diuretics during their pregnancy were excluded from the comparison of echocardiographic changes among these 4 periods.

Ventricular dimensions, such as left ventricular end-diastolic diameter (LVDd), left ventricular end-systolic diameter (LVDs), and right ventricular end-diastolic diameter (RVDd), were measured from M-mode echocardiography in the parasternal long- or short-axis views. Percent fractional shortening (%FS) was calculated from the LVDd and LVDs. Right ventricular size was graded retrospectively as normal or mildly, moderately or severely enlarged on the parasternal long- and short-axis views and from the apical 4-chamber, 2-chamber and long-axis views by 1 skilled ultrasonographer who was also blinded to the study. Outflow obstruction, valvular regurgitation, and systolic pulmonary artery pressures were quantified using Doppler echocardiographic techniques.[7,8] Pulmonary regurgitation (PR) was graded as mild, moderate or severe based on the appearance of the regurgitant jet on color-flow Doppler imaging. Pulmonary stenosis (PS) was defined as above moderate when the Doppler-derived systolic pressure gradient across the pulmonary valve was ≥50 mmHg.[9]

Statistical Analysis

Statistical significance was evaluated using paired and unpaired Student's t-tests for comparisons between means. A chi-squared test and Fisher's exact test were used for categorical data. All data are expressed as the mean±standard deviation. Statistical significance was defined as a P-value <0.05. The SPSS 11.0 software package (SPSS, Chicago, IL, USA) was used for statistical analysis.

Table 1. **Clinical Course of Obstetric Patients With Cardiac Events**

	Age (years)	History of delivery	NYHA class	History of reoperation/ arrhythmia/medication	Residual lesion	Pregnancy-associated events
1	34	0P	II–III	VSD closure+TVR+PVR PSVT p/o ABL β-blocker+diuretics for PSVT and HF	Small VSD, Moderate TS	20W~PSVT↑⇒antiarrhythmic agent 30W: complicated with PIH 32W: bigeminal PVC with BP fall, right HF (severe TS) after CS
2	33	2P	I	PSVT p/o ABL	Moderate PR	26W~NYHA II⇒diuretics 28W~PSVT↑, NSVT
3	28	1P	I	None	Moderate PS, Moderate PR	33W~PS severe 36W: excessive edema after delivery ⇒diuretics
4	32	1P	I	PMI for CAVB	Severe PR	34W~NYHA II, excessive edema⇒diuretics 35W: NSVT
5	35	1P	I	LV-RA communication closure AFL/AT p/o ABL Ia antiarrhythmic agent+verapamil +β-blocker for AT	Moderate PR	9W~AT↑⇒β-blocker↑ 13W~NYHA II, CTR↑⇒diuretics
6	27	0P	II–III	re-RVOTR β-blocker for AT, NSVT	Left PA obstruction	32W~NYHA II, CTR↑, moderate TR 34W: TR↑, CVP↑ after CS⇒diuretics
7	28	1P	I	None	Moderate PR	18W: rapid NSVT⇒β-blocker

NYHA, New York Heart Association; VSD, ventricular septal defect; TVR, tricuspid valve replacement; PVR, pulmonary valve replacement; PSVT, paroxysmal supraventricular tachycardia; p/o, post of; ABL, ablation; HF, heart failure; TS, tricuspid stenosis; PIH, pregnancy-induced hypertension; PVC, premature ventricular contraction; BP, blood pressure; CS, cesarian section; PR, pulmonary regurgitation; PMI, pacemaker implantation; CAVB, complete atrioventricular block; LV-RA, left ventricle-right atrium; AFL, atrial flutter; AT, atrial tachycardia; CTR, cardiothoracic ratio; RVOTR, right ventricle outflow reconstruction; PA, pulmonary artery; TR, tricuspid regurgitation; CVP, central venous pressure.

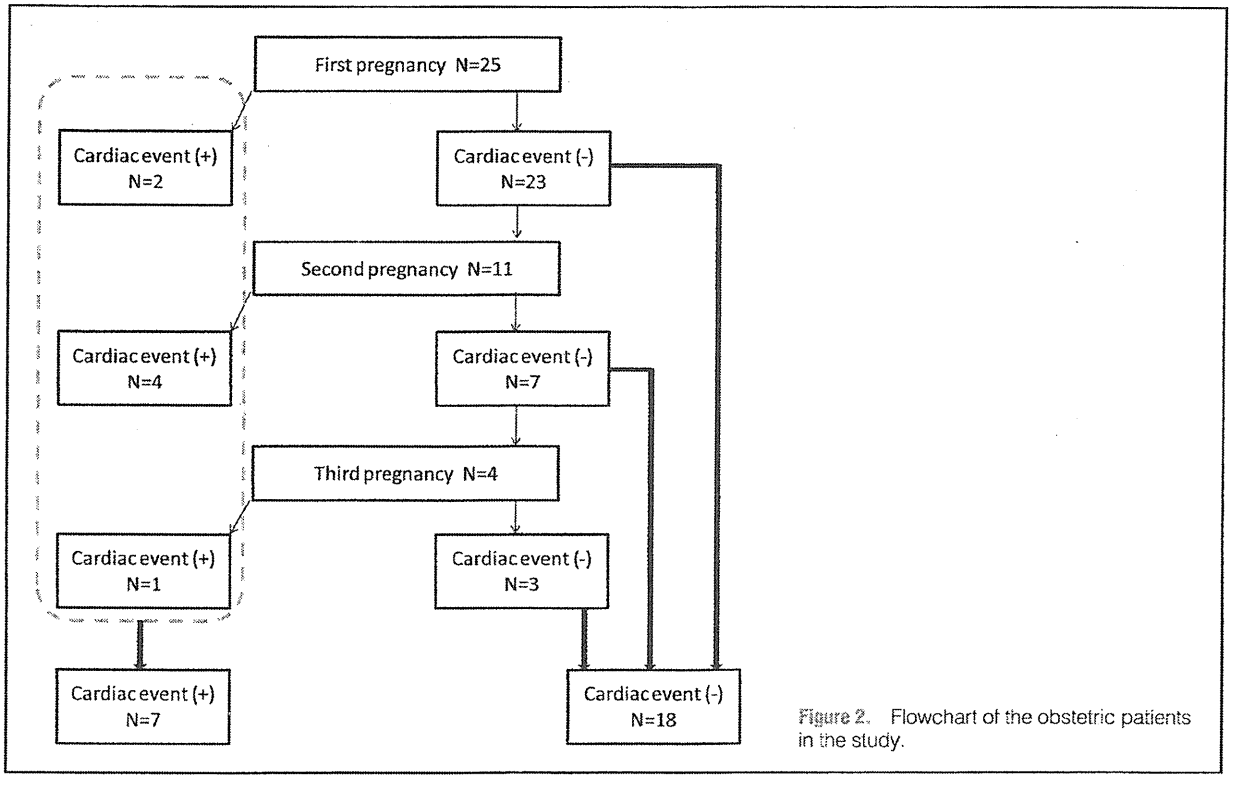

Figure 2. Flowchart of the obstetric patients in the study.

Results

Characteristics of Patients

The 25 women with repaired TOF completed 40 pregnancies in our hospital from 1987 to April 2010. The number of deliveries complicated with repaired TOF showed a particular increase after the year 2000 (Figure 1); 21 patients were initially diagnosed with TOF, 3 with TOF and pulmonary atresia (PA), and 1 with TOF, PA and a major aortopulmonary collateral artery (MAPCA). One patient was complicated by hypertrophic cardiomyopathy. All patients underwent reparative surgery, including 7 who had a Blalock-Taussig shunt operation before TOF repair. The mean age at repair was 7.1 years (range: 1–36 years); 4 patients required reoperation: 2

Table 2. Comparison of Obstetric Patients With and Without Cardiac Events

	Cardiac events (+)	Cardiac events (−)	P value
Age at repair operation (years)	4.7±5.0	8.0±9.6	0.58
Age at delivery (years)	31.3±3.3	30.0±5.3	0.40
Duration between repair to delivery (years)	26.6±4.8	22.0±7.9	0.18
Smoking	2	1	0.18
Multipara	5	6	0.18
NYHA ≥II	2	0	0.07
History of reoperation	3	1	0.052
History of supraventricular tachycardia	3	0	0.003
Pre-pregnancy use of medication	3	1	0.052
CTR before pregnancy or during first trimester (%)	63.5±9.2	53.4±5.5	0.04
QRS duration before pregnancy or during first trimester (ms)	135±27	110±28	0.07
Right heart dilatation before pregnancy or during first trimester	6	11	0.36
RVDd before pregnancy or during first trimester (mm)	35.6±14.7	28.8±4.3	0.36
PR ≥moderate	5	10	0.67
PS ≥moderate	1	1	0.49
BNP level before pregnancy or during first trimester (pg/ml)	42±29	31±23	0.64
Peak BNP level after second trimester (pg/dl)	97±41	48±13	0.01
Weeks of delivery	35.7±3.2	38.3±1.5	0.084
Cesarian section	4	5	0.20
Neonatal birth weight (g)	2,262±590	2,742±423	0.03

RVDd, right ventricle end-diastolic diameter; PS, pulmonary stenosis; BNP, brain natriuretic peptide. Other abbreviations see in Table 1.

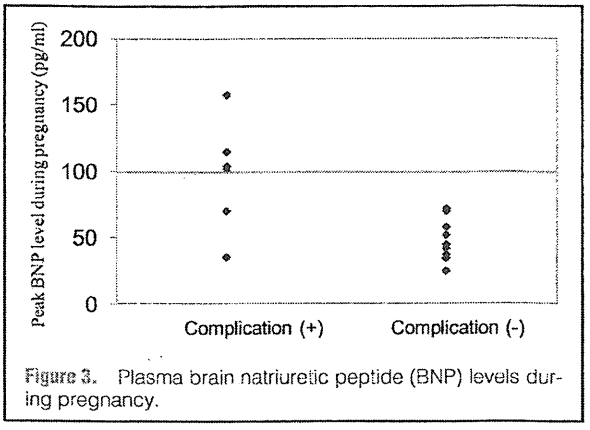

Figure 3. Plasma brain natriuretic peptide (BNP) levels during pregnancy.

for right ventricular outflow tract reconstruction, 1 for patch closure for residual VSD and tricuspid valve replacement, and 1 for patch closure for LV-RA communication. Another patient underwent percutaneous transluminal angioplasty for left pulmonary artery stenosis twice before her pregnancy. Three patients had a pacemaker implanted for advanced atrioventricular block and another 3 had a history of catheter ablation for supraventricular tachycardia (SVT). Two patients had a residual VSD and 1 had left pulmonary artery occlusion. Moderate to severe PR was present in 15 patients, and moderate to severe PS was found in 2 patients. One patient had moderate tricuspid stenosis after tricuspid valve replacement.

With regard to NYHA class, 23 patients were in class I before pregnancy and 2 were in classes II–III. Four patients were prescribed medications before pregnancy: diuretics in 1 patient, an antiarrhythmia drug in 1, and both in 2. All 4 patients continued these medications during pregnancy. Two patients stopped taking angiotensin converting enzyme inhibiters before or immediately after pregnancy. Three patients had a smoking habit.

Pregnancy Course

The mean age at delivery was 29.1 years (range: 20–39 years); 14 patients had 1 delivery, 7 had 2 deliveries, and 4 had 3 deliveries. All pregnancies were singletons. All patients delivered successfully at a mean of 37.8 weeks of gestation (range: 30–41 weeks). There were 29 vaginal deliveries and 11 deliveries by CS. The reasons for CS were 1 case of maternal heart failure, 1 of PIH, 3 of fetal distress, 1 of arrest of labor, 3 of breech presentation, and 2 of repeated CS. Among the vaginal deliveries, 26 occurred under epidural anesthesia, and 1 and 2 antibiotics were used in 28 and 12 deliveries, respectively, for prophylaxis against endocarditis.

Cardiac Events

Cardiac events occurred in 7 of 40 deliveries (17.5%) in 7 patients (28%): 1 case of new onset of non-sustained ventricular tachycardia (NSVT) requiring treatment, 2 of heart failure, and 4 of worsening heart failure and arrhythmias including SVT and NSVT. Endocarditis and thromboembolic events did not occur. The clinical courses of patients complicated with cardiac events are shown in Table 1; 1 patient had TOF with PA and another had TOF with PA and MAPCA; 2 patients had cardiac events in the first pregnancy and none in later pregnancies, 4 had cardiac events in the second pregnancy, and 1 had a cardiac event in the third pregnancy (Figure 2).

Comparison of Patients With and Without Cardiac Events

A comparison of patients with and without pregnancy-associated cardiac events is shown in Table 2. A history of ablation for SVT and larger CTR within 1 year before pregnancy or during the first trimester were more frequent in patients with cardiac events. BNP levels (normal range <18.4 pg/ml) were

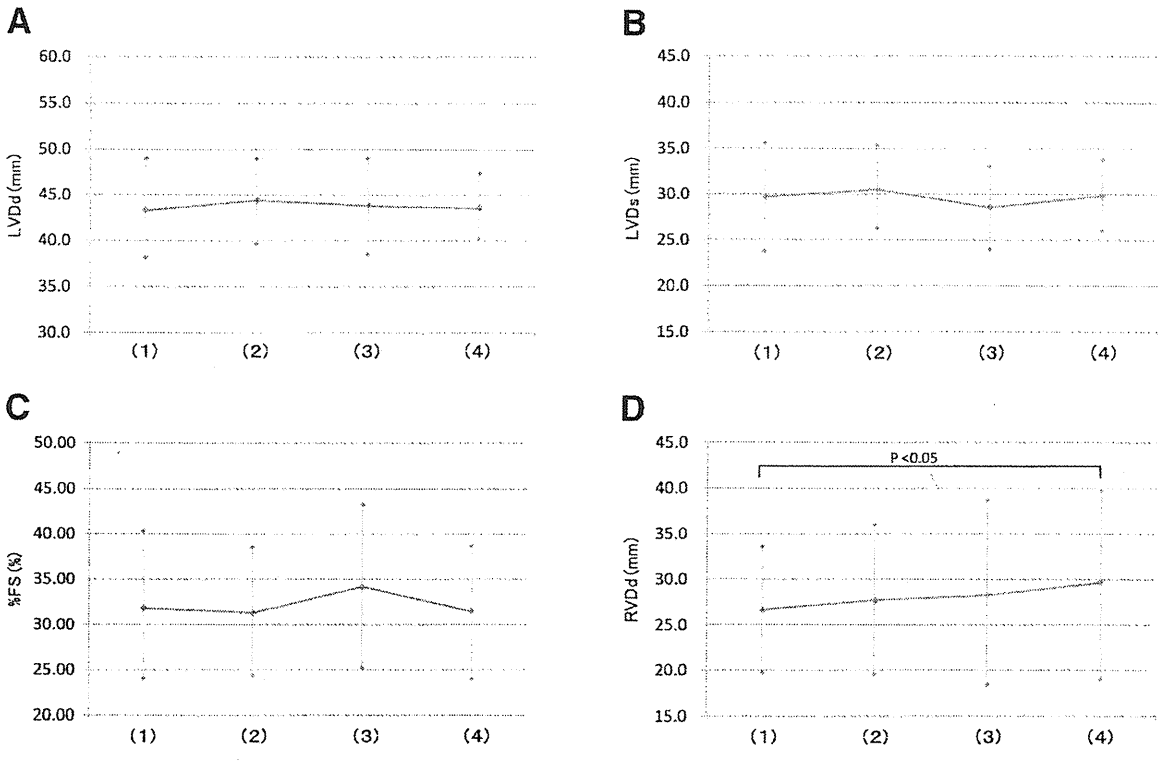

Figure 4. Changes in the echocardiographic parameters. The numbers on the horizontal axis are: (1) within 1 year before pregnancy to the first trimester, (2) in the second and third trimester (from 14 weeks of gestation to delivery), (3) after delivery to 1 month postpartum, (4) from 6 months to 1 year after delivery. LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; FS, fractional shortening; RVDd, right ventricular end-diastolic diameter.

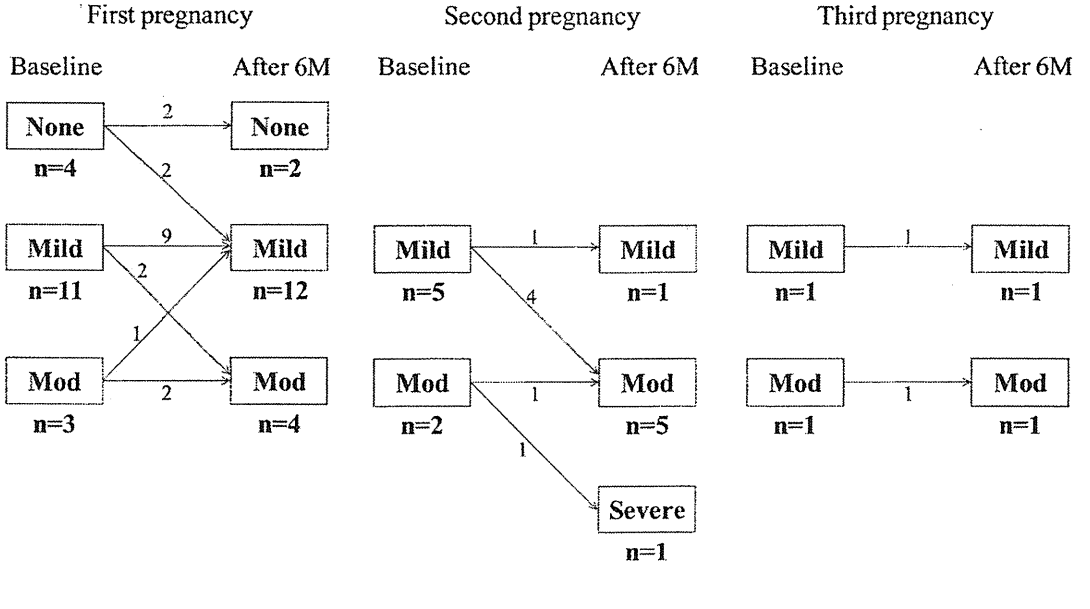

Figure 5. Increased right heart dilation after each pregnancy.

measured during 15 pregnancies. Baseline BNP levels did not differ significantly between patients with and without cardiac events. However, peak BNP levels after second trimester were significantly higher in patients with cardiac events, with BNP >100 pg/ml in some of these patients (Figure 3).

Obstetric Events

Two patients were complicated with PIH: 1 had bigeminal premature ventricular contraction, and then BP fall after emergency CS because of PIH, and thus she was also included in the patients with cardiac events (Table 1, patient 1). There were 9 premature deliveries in 8 patients, because of maternal heart failure in 3 cases, premature rupture of membranes in 2, threatened premature labor in 3, and PIH in 1. Therefore, the mean weeks of delivery was shorter in patients with cardiac events than in those without cardiac events, but the difference was not significant. Of the 29 vaginal deliveries, 14 (48.2%) were complicated with postpartum hemorrhage. In contrast, none of the 11 CS deliveries resulted in postpartum hemorrhage. No patient needed a blood transfusion after delivery.

Offspring Events

There were no neonatal deaths. The mean birth weight was 2,665 g and was significantly lower for offspring of patients with cardiac events (Table 2). Two neonates (5.0%) were SGA, including 1 whose mother smoked during pregnancy and 1 whose mother took β-blockers for her history of NSVT; 2 had TOF, 1 had VSD, and 1 had atrial septal defect. Their 3 mothers had TOF without PA or right aortic arch. No patients were tested for genetic conditions.

Changes in Echocardiographic Parameters

Changes in the mean LVDd, LVDs, %FS, and RVDd during the perinatal period are shown in Figure 4. Mean RVDd was 26.7±6.9 mm within 1 year before pregnancy to the first trimester, 27.7±8.9 mm in the second and third trimester, 28.2±10.1 mm after delivery to 1 month postpartum, and 29.6±10.2 mm at 6 months to 1 year after delivery. RVDd at 6 months to 1 year after delivery became significantly greater than that within 1 year before pregnancy to the first trimester. Right ventricular size was able to graded retrospectively in 24 pregnancies and the changes after each pregnancy are shown in Figure 5. Right heart dilatation tended not to recover after pregnancy and to progress with each pregnancy.

Discussion

Our data suggest that most pregnancies in patients with repaired TOF have a favorable outcome, which is compatible with previous reports. Rates of 7–12% have been reported for maternal cardiac events during pregnancy after repaired TOF,[1,2,10–12] and the rate in this study was 17.5%. The reasons of our higher rate of maternal cardiac events may be (1) inclusion of patients with PA and/or MAPCA in the study and (2) the hospital is a referral hospital. Left ventricular dysfunction, severe pulmonary hypertension, decreased subpulmonary ventricular ejection fraction and/or severe PR,[4] use of cardiac medication pre-pregnancy, history of arrhythmia, and prior pulmonary valve replacement[10] have been proposed as predictors of maternal cardiac events during pregnancy. In our study, the predictors of maternal cardiac events were a history of ablation for SVT and large CTR on chest radiograph. This is the first report to show the potential value of chest radiography for predicting maternal cardiac events. Because the number of patients was small, NYHA class ≥II, history of reoperation, use of medication pre-pregnancy, and wider QRS duration on ECG did not reach a significant level as risk factors for cardiac events, we were unable to perform a multivariate analysis of pregnancy-associated risk factors. Moreover, RV dilatation, RVDd, and over-moderate PR on echocardiography were not significantly different between patients with and without cardiac events, whereas CTR reflecting an enlarged right heart was significantly different. We have to consider that the efficacy of echocardiography was not adequate to assess the right heart. A further study is required to investigate these factors.

Management of patients late after repair of TOF has recently focused on the risk of arrhythmia and sudden cardiac death.[13] A Japanese multicenter study of the incidence, manifestation and management of arrhythmia in congenital heart disease during pregnancy found that SVT tended to require antiarrhythmic agents more frequently than ventricular arrhythmia.[14] The current study results clearly show the importance of a prior history of SVT in the evaluation of the risk of pregnancy. PR and progressive dilation of the RV are closely related to SVT and sudden death.[15] Moreover, heart rate variability, which is a significant marker of autonomic nervous function and may predict tachyarrhythmia, may be significantly impaired in pregnant women after repair of congenital heart disease.[16] An arrhythmogenic effect could cause significant hemodynamic compromise in both the mother and fetus in women with repaired TOF with subclinical LV intolerance and RV dilation during pregnancy.[17,18] Therefore, arrhythmia and an enlarged RV should be viewed with particular caution in the pregnancy management of these women.

BNP is useful biomarker for the assessment of congestive heart failure in congenital heart disease, as well as other heart diseases.[19] Tanous et al measured the BNP levels in 66 women with heart disease and found that those with events during pregnancy (n=8) had BNP >100 pg/ml, whereas no women with BNP ≤100 pg/ml had adverse events (negative predictive value: 100%).[20] In our study, in which we followed BNP levels in 15 patients, several of those with cardiac events showed a peak BNP level ≤100 pg/ml. BNP levels at baseline did not predict cardiac events, and the timing of the examination of BNP level after second trimester was similar to the timing for the manifestation of heart failure. Thus, we consider BNP levels not as a predictor of heart failure, but as a useful marker to identify and to manage these obstetric patients.

Ventricular size and function assessed by cardiac magnetic resonance imaging (MRI) are good predictors for major adverse clinical outcomes in patients late after repair of TOF.[21] Because the current study showed that RVDd on routine echocardiographic examination was not an excellent predictor of cardiac events, MRI may be more applicable for screening to assess the risk of pregnancy in severely affected patients.

Japanese guidelines for the indication and management of pregnancy and delivery in women with heart disease recommend the use of antibiotic prophylaxis at the time of delivery for patients with repaired cyanotic heart diseases, including TOF. All patients in our study received antibiotic prophylaxis against endocarditis, and there was no occurrence of endocarditis. The incidence of PIH was 5%, which is similar to that in the Japanese general population (4%).[22] Because one of the patients with PIH had a BP fall from a bigeminal pulse, obstetric events such as PIH may cause fetomaternal morbidity in patients with repaired TOF to a greater extent than in the general population.

In our study population, postpartum hemorrhage occurred in approximately half of the women after vaginal delivery, which is a much higher rate than the 8.8% in a previous report.[11]

Asian race, antenatal hospitalization, induction of labor, and epidural anesthesia have been suggested as risk factors for postpartum hemorrhage after vaginal delivery.[23,24] Because many of the patients were delivered by induction under epidural anesthesia, the rate of postpartum hemorrhage might have been increased. Careful management of atonic bleeding is required, especially after vaginal delivery in patients with repaired TOF.

The risk of recurrence of congenital heart disease in women with repaired TOF has been reported to range from 0% to 9.8%.[1–3,25,26] The recurrence rate in our patients was approximately 10%, which is close to the rate of 9.8% in the study by Pedersen et al. in which it was also pointed out that the rate of congenital cardiac disease in the offspring was 4.8%, excluding siblings with chromosome 22q11.2 deletion syndrome.[3] We did not perform genetic tests in our patients and it is possible that some of the patients had a genetic condition. However, all 3 mothers whose children showed congenital heart disease in this study were not TOF with PA and right aortic arch, which suggests the incidence of chromosome 22q11.2 deletion syndrome.

Regarding cardiac size, Uebing et al reported that pregnancy itself was associated with a persistent increase in subpulmonary ventricular size in patients with repaired TOF,[27] using an analysis that did not take the number of deliveries into consideration. Our data suggest that the right heart tends to be more and more dilated after the second and third deliveries, which indicates that pregnancy can affect long-term prognosis in patients with repaired TOF. Clarification of the long-term effects of pregnancy in these patients requires a long-term observational study to compare patients with and without a history of pregnancy. In general, the number of pregnancies complicated with repaired TOF is increasing and further studies are required to establish better management to minimize the risk of pregnancy and give a better long-term prognosis.

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Disclosures

None.

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手術を受けていない成人先天性心疾患に対する心エコー

妊娠・出産に対する心エコー

軽症で手術適応がない先天性心疾患患者においては，妊娠・出産のリスクは一般に大きくない．しかしながら，一部の疾患においては心内膜炎や奇異性塞栓，大動脈拡張，妊娠高血圧症の合併などへの特別な注意が必要である．適応があるが，手術未施行である場合，重症で手術適応がない患者においては，リスクも高く，慎重な周産期管理が必要である．心エコー検査は非侵襲的で胎児被曝を与えない，妊娠中に最も適した心血管検査である．

神谷 千津子
国立循環器病研究センター周産期・婦人科
池田 智明
三重大学医学部産科婦人科学教室

Komiya, Chizuko
平成13年名古屋大学医学部卒業．平成15年より国立循環器病センター心臓血管内科レジデント，専門修練医課程を修了後，平成20年より同センター周産期・婦人科スタッフとなり，循環器疾患合併妊娠や周産期(産褥)心筋症をはじめとして，循環器科と産婦人科にまたがる新たな専門分野に取り組んでいます．

●はじめに

手術を受けていない(手術未施行例の)成人先天性心疾患合併妊婦には，① 軽症で手術適応がないと診断されている，② 手術リスクが高く，適応がないと診断されている(Eisenmenger症候群など)，③ 手術適応があるが，本人・家族の意向や医療機関の未受診などにより未施行のままでいる，④ 妊娠中に初めて先天性心疾患が見つかる，などさまざまな背景が考えられる．そこで，個々の病態・重症度に応じた適切な周産期管理が必要となる．よりよい母児管理のためには，産科，循環器科，小児循環器科，麻酔科，心臓外科などが密接に連携した診療体制の構築が必須である．

●周産期における循環動態の変化と心血管疾患合併母体への影響

妊娠分娩産褥期には，母体の循環動態はダイナミックに変化する．心血管疾患合併妊娠においては，以下のような循環生理を踏まえ，周産期管理を行う．

・**循環血漿量の増大**：循環血漿量は妊娠初期から中期にかけて大きく増加し，平均して非妊時の1.5倍となる．このような容量負荷の増大に対して，狭窄性疾患や肺高血圧症，心機能低下症例では心不全の出現や低心拍出量に注意していく必要がある．

また，分娩時には，酸素消費量が約3倍となり，陣痛に伴う子宮収縮によって静脈還流量が300～500ml/増加，心拍出量は15～25%増加する．分娩直後速やかに子宮が収縮するとともに，妊娠後半の子宮による下大静脈の圧迫が解除され，急激な静脈還流の増大が起こる．妊娠中に増加した循環血漿量のため，分娩後は一過性に容量負荷の状態をきたし，正常化するまでには約4～6週間かかる．心血管合併妊娠において最も母体死亡率が高いのが産褥期であり，特別な注意が必要である．

・**血管抵抗の低下**：妊娠初期より大動脈圧，全身血管抵抗は低下し，妊娠中期には最低値をとる．このような圧負荷軽減により，中等度以下の逆流性疾患やシャント疾患では問題なく妊娠出産を終えることが多い．

・**凝固能の亢進**：妊娠中は凝固因子などが増加し，活性化されるため，血栓・塞栓のリスクが高くなる．深部静脈血栓(DVT)や肺塞栓の発症，人工機械弁置換術後例では血栓形成による弁機能不全や塞栓症の合併が起きやすいため，綿密な抗凝固・抗血小板療法が必要である．

・**心拍数の増加**：心拍出量の増加は，妊娠初期～中期には主に一回心拍出量の増加により，妊娠中期

Key Sentence

- 妊娠は心循環器系に大きな変化をもたらすが，循環血漿量増加による前負荷の増大と，血管抵抗低下による後負荷の減少が，その二大要素である．
- 軽症から中等度の左右短絡疾患では，血管抵抗の減少により血液量増加と釣り合いがとれ，ほとんどの場合で合併症なく妊娠分娩を終えることができる．
- 妊娠・産褥期には凝固活性が増加するため，静脈血栓症や奇異性塞栓症に注意が必要．
- Marfan症候群，大動脈二尖弁，大動脈縮窄などの合併妊娠においては，妊娠中に大動脈瘤拡大・解離を認めることがあり，注意が必要である．
- 大動脈縮窄においては，妊娠高血圧症候群の合併率が高いことが知られている．

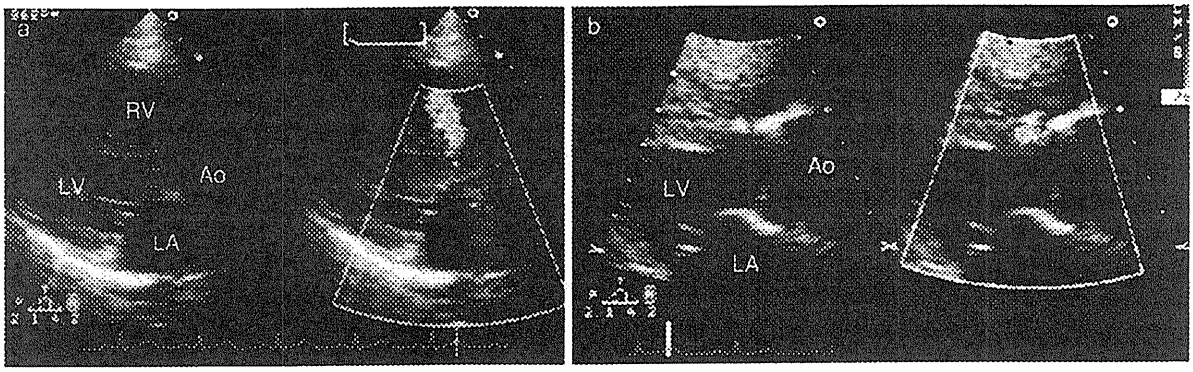

図1　VSD症例における妊娠・産褥期心エコー所見
初回妊娠中，心雑音にて初めてsmall VSDと診断された．妊娠後期(a)と産褥1年(b)のシャント血流像であるが，妊娠中に増加していることがわかる．小児期に心不全を起こさず，妊娠期に発見されるような未手術のVSD症例は，右室梁透視による有意な大動脈弁閉鎖不全がある場合を除いて，妊娠時の問題は少ない．
RV：右室，LV：左室，Ao：大動脈，LA：左房

～後期には心拍数の増加により達成される．妊娠後期には，妊娠前の約20％程度まで心拍数は増加する．心拍数の増加や血液量の増加に伴う心拡大(心筋伸展)に伴い，不整脈の出現も増加する．

・血管壁の脆弱性増加：妊娠中，エストロゲンなどの影響で大動脈壁は中膜の変性をきたし，脆弱性を増す．大動脈拡大を伴うMarfan症候群，大動脈炎症候群や大動脈縮窄・大動脈二尖弁患者では大動脈瘤拡大や大動脈解離のリスクが上昇する．

●症例ごとにみる手術未施行例の成人先天性心疾患と妊娠・出産

(1) 非チアノーゼ性心疾患

(a) 左右短絡疾患

心房中隔欠損(ASD)，心室中隔欠損(VSD)，卵円孔開存(PFO)，動脈管開存(PDA)などの左右短絡疾患では，妊娠による血液量の増大に伴って心雑音が大きくなり，初めて診断される場合がある(図1)．当院におけるVSD・ASD妊娠におけるエコー計測によるQp/Qs(肺体血流比)の変化を表1にあげる[1]．多くの場合，妊娠中にシャント量は増大するが，シャント量が多い症例でも，末梢血管抵抗の減少により血液量増加と釣り合いがとれ，ほとんどの場合で心不全の合併なく妊娠出産を終えることができるが，正常妊娠よりも流産や早産のリスクが若干高くなることが知られている．

症例1：ASD．28歳，初産婦．16歳時にASDと診断され，経過観察されていた．20歳ごろより閃輝性暗点を伴う強い片頭痛がたびたび出現した．27歳，両手レイノー現象のエピソードが数回あり，ASD

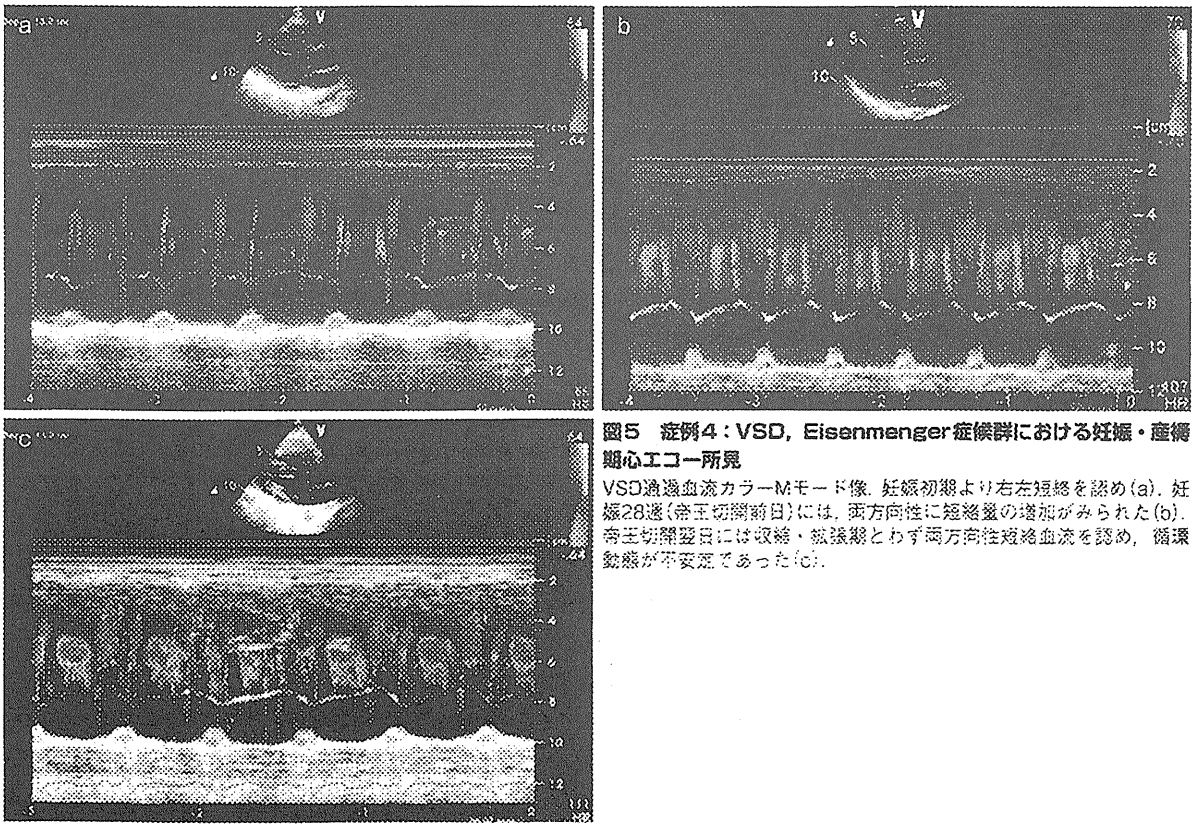

図5　症例4：VSD，Eisenmenger症候群における妊娠・産褥期心エコー所見

VSD通過血流カラーMモード像．妊娠初期より右左短絡を認め(a)，妊娠28週(帝王切開前日)には，両方向性に短絡量の増加がみられた(b)．帝王切開翌日には収縮・拡張期とわず両方向性短絡血流を認め，循環動態が不安定であった(c)．

や解離の発症リスクが高くなる．大動脈弁輪径が44mm以上の症例では，置換術をしないと妊娠は禁忌である．40～44mmでもリスクは高いが，本人が希望すれば，保存的に観察しながら(1～2週間に1回のエコー)，妊娠・出産が可能である．40mm未満であれば，通常分娩が可能である．分娩においては，血圧・疼痛管理が最重要である[9]．

(a) 大動脈縮窄

大動脈縮窄(CoA)未修復例は妊娠中に高血圧，左心不全，さらに大動脈瘤形成や解離などの重大な合併症が認められることがあり，特に圧較差30mmHg以上の症例でリスクが高いとされる[10]．大動脈拡張を伴い，妊娠中に高血圧を合併する場合は，安静，収縮期圧を140mmHg以下に保つことを目標とし，β遮断薬投与を行う．しかし，血圧が下がりすぎると胎盤血流が減少するため，定期的な血圧測定が必要である．

症例5：CoA．28歳，初産婦．生後VSDを指摘され，1歳時に閉鎖術を施行．2歳時に術後評価のために行った心臓カテーテル検査で，圧較差20mmHgのCoAを指摘された．自覚症状なく経過したが，25歳時よりエコー上の圧較差が40mmHgを超えるようになり，トレッドミル検査では，軽労作で収縮期血圧が200mmHg以上に上昇した．CoAに対する治療を考慮中に妊娠され，当科紹介．24時間血圧測定上，安静時には収縮期血圧110～120mmHg台で安定していたが，軽労作で180mmHg台への上昇を認めた．また，片頭痛の訴えもあり，血圧上昇を予防する目的でカルベジロール内服を開始した．婦人科合併症もあり，妊娠34週で選択的帝王切開術を施行．術後合併症なく経過した(図6)．

●おわりに

ほとんどの手術未施行例の成人先天性心疾患合併妊娠が，合併症なく妊娠・分娩を終える一方，Eisenmenger症候群や大動脈瘤を合併したMarfan症候群患者など，母体の命にかかわる重症疾患も

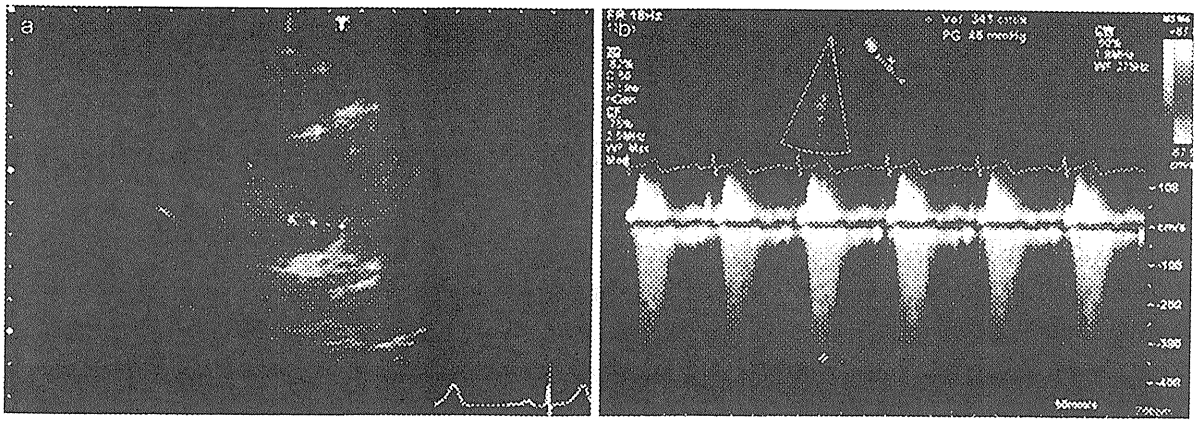

図6　症例5：CoA症例における妊娠初期の心エコー所見
妊娠初期は左鎖骨下動脈分岐後大動脈径 9mm(a)であり，狭窄部の推定圧較差は46mmHg(b)であった．安静，β遮断薬内服にて，妊娠経過中，圧較差はほぼ変わらなかった．

あり，個別の対応が必要とされる．また，見落とされがちであるが，最も危険度が高い時期は産褥期であり，分娩が無事終わったからと安心せずに，産後も適切に経過観察を行っていく診療体制づくりが重要であろう．

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ORIGINAL ARTICLE

Risk factors for maternal outcome in pregnancy complicated with dilated cardiomyopathy

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Objective: The goal of the study was to determine risk factors for maternal cardiac failure in pregnancy complicated with dilated cardiomyopathy (DCM).

Study Design: The subjects were 29 patients diagnosed with DCM before conception or during the first 7 months of pregnancy. DCM was defined as left ventricle end-diastolic dimension (LVDd) $\geqslant$48 mm and/or fractional shortening (%FS) $\leqslant$30% on echocardiography. Patients were followed until at least 1 year after delivery and were categorized into a poor prognosis group ($n=6$; death or end stage heart failure of New York Heart Association (NYHA) class III and IV) and a good prognosis group ($n=23$; all other cases).

Result: DCM was initially diagnosed during pregnancy in 6/6 and 8/23 patients in the poor and good prognosis groups, respectively ($P<0.005$). The %FS of the first test during pregnancy was 17.5 ± 6.2 and 27.4 ± 9.3% in the respective groups ($P<0.005$). In eight abortion cases with %FS 15.2 ± 3.1%, %FS, cardiac function and NYHA class were maintained until 20 months after abortion. There was no relationship between LVDd and maternal outcome.

Conclusion: Onset during pregnancy and decreased %FS are risk factors for a poor maternal outcome in patients with DCM. Abortion prevents further deterioration of cardiac function in patients with a very low %FS.
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Keywords: dilated cardiomyopathy; pregnancy; prognosis; cardiac function

Introduction

Dilated cardiomyopathy (DCM) is characterized by ventricular enlargement and systolic cardiac dysfunction, especially on the left side.[1] In association with pregnancy, there are two types of DCM: peripartum cardiomyopathy (PPCM) and DCM not categorized as PPCM.[2,3] PPCM is distinguishable from DCM-complicated pregnancy by the time of onset, as PPCM is defined as occurring in the last month of pregnancy until 5 months after delivery and by the causal relationship, with PPCM exclusively associated with cardiac lesions such as valve or coronary disease.[4,5] Elkayam *et al.*[3] defined 'pregnancy-associated (PA) cardiomyopathy' as a condition that occurred during pregnancy except in the last month and reported similar clinical characteristics to those of PPCM. Morales *et al.*[6] found common genetic mutations in PPCM and DCM. At present, however, PPCM and DCM-complicated pregnancy are considered to be different disorders.

There have been many studies of the etiology,[7] epidemiology,[8] prognosis[9] and treatment[10] of PPCM, but only a few studies of DCM-complicated pregnancy.[11,12] Bernstein and Magriples[12] compared the cardiac outcomes of DCM-complicated pregnancy with PPCM and Grewal *et al.*[11] compared similar outcomes in cases of DCM, with and without pregnancy. DCM-complicated pregnancy showed a better prognosis than PPCM, but a worse prognosis than non-pregnant DCM. These results indicate a negative impact of pregnancy on the cardiac outcome of DCM. Therefore, the current retrospective study of DCM-complicated pregnancy was carried out to determine parameters that are significantly associated with cardiac outcome at 1 year after delivery, to examine whether early termination of pregnancy preserves cardiac function and to establish whether the outcome of PA DCM is worse than that of pre-pregnancy DCM.

Methods

We examined the records of 29 women with DCM who were pregnant from January 1982 to December 2007 and visited the National Cerebral and Cardiovascular Center in Japan. DCM was defined as left ventricle end-diastolic dimension (LVDd) $\geqslant$48 mm and/or fractional shortening (%FS) $\leqslant$30% on echocardiography, using one of the criteria for PPCM published by the Journal of the American Medical Association.[5,13,14] Patients with PPCM defined by

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Demakis' criteria of (1) development of cardiac failure in the last month of pregnancy or within 5 months of delivery, (2) absence of a determinable etiology for the cardiac failure and (3) absence of demonstrable heart disease before the last month of pregnancy were excluded.[4] Those with structural heart disease and secondary LV dysfunction were also excluded.[5,13,14]

The 29 women (29 pregnancies) were followed until 1 year after delivery. Artificial abortion cases were followed until at least 20 months after abortion to match the time course of delivery cases. Echocardiography was performed at least once in each trimester to evaluate cardiac function, with a focus on LV %FS and LVDd. Demographic data were collected from each patient's chart for maternal age, parity, presence or absence of hypertension, diabetes mellitus, history of multiple pregnancies and body mass index. For pregnancy data, the delivery mode (Cesarean section or vaginal delivery), gestational weeks of delivery, birth weight and the infant's prognosis were collected. Changes of %FS, LVDd and QJ;New York Heart Association (NYHA) classification were also investigated. Patients with cardiac dysfunction and marked limitation of physical activity were defined as having heart failure.

Patients who died or had end stage heart failure of NYHA class III and IV were placed in a poor prognosis group ($n=6$). All other patients were placed in the good prognosis group ($n=23$). The 29 cases were also categorized into two groups based on the timing of the initial diagnosis of DCM, the PA and non-PA groups. Patients in the PA group had DCM diagnosed during the first 8 months of pregnancy, whereas those in the non-PA group had been diagnosed with DCM before pregnancy.

Hypertension was defined as systolic blood pressure $\geqslant 140$ mm Hg or diastolic blood pressure $\geqslant 90$ mm Hg or a requirement for antihypertensive agents.[15] Diabetes mellitus was defined as the presence of a fasting plasma glucose level $\geqslant 126$ mg dl^{-1}, a hemoglobin type A1c fraction $\geqslant 6.5\%$, a plasma glucose level $\geqslant 95$, $\geqslant 180$ and $\geqslant 155$ mg dl^{-1}, before and 1 and 2 h after a 75 g oral glucose tolerance test, respectively (a patient meeting two of these three criteria was judged to be positive); or a requirement for antidiabetic drugs.[16]

The study was exempted from Committee on Human Research approval (National Cerebral and Cardiovascular Center), because there no longer exists a key or code sheet relating the identity of each patient to his or her private health information.

Statistical analysis

For continuous variables, a Student's *t*-test was performed for analysis of normally distributed data and a Wilcoxon test was used for data that were not normally distributed. χ^2-test and Fisher's exact test were performed for comparing categorical variables between the two groups. All statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC, USA). A *P*-value of 0.05 was considered statistically significant.

Results

Comparison of PA DCM and non-PA DCM

Among the 29 subjects, there were 14 cases of PA DCM and 15 cases of non-PA DCM (Table 1). Of the 14 cases of PA DCM, 12 were diagnosed in the first trimester and 2 in the second trimester. Ten of the PA DCM cases presented with general fatigue and dyspnea on light exertion, two had night dyspnea and two had dyspnea and increasing leg and pretibial edema. All cases were diagnosed as DCM by echocardiography. The cases of non-PA DCM were diagnosed at a median age of 16 years, at 6 months old in two cases, at 2 to 3 years old in four cases, at 12 to 20 years old in five cases and at 20 to 30 years old in four cases. DCM had been confirmed before the first conception in all these cases. During pregnancy the first echo was performed in the first trimester in all cases. The %FS was significantly lower in the PA group than in the non-PA group (17.5 versus 27.4%, $P<0.005$). The LVDd was larger in the PA group, but the difference was not significant ($P=0.15$), and the incidence of heart failure was significantly higher in the PA group (6/14 versus 0/15, $P<0.005$; Table 2). The gestational weeks of delivery and birth weight of the newborn were both significantly lower in the PA group (34.0 ± 3.5 versus 37.8 ± 1.0 weeks, $P<0.01$; 2146 ± 579 versus 2815 ± 352 g, $P<.01$).

Comparison of cases with poor and good prognoses

More cases in the good prognosis group had %FS $\geqslant 22\%$ throughout the observed course, compared with the poor prognosis group (14/15 (93%) versus 0/6 (0%), $P<0.0001$) (Figure 1). In the

Table 1 Clinical characteristics of PA and non-PA cases

	PA (n = 14)	*Non-PA (n = 15)*
Induced abortion	4	4
Age (median, range)	30, 22–41	24, 24–33
Multiparous	8	5
Medications		
Beta blockers	2	4
Diuretics	1	3
%FS (%)[a]	17.5 ± 6.2	27.4 ± 9.3
LVDd (mm)	57.8 ± 4.6	53.4 ± 4.1
Hypertension	4	3
Diabetes mellitus	1	1
Multiple pregnancy	0	0
Body mass index	26.2 ± 3.3	26.4 ± 4.5

Abbreviations: PA, pregnancy-associated (DCM occurred in the first 7 months of pregnancy); non-PA, non-pregnancy associated (DCM occurred before pregnancy); NYHA, New York Heart Association; %FS, percent fractional shortening; LVDd, left ventricle diastolic dimension.

[a]The %FS of the first test during pregnancy was significantly lower in PA cases than in non-PA cases (17.5 versus 27.4%, $P<0.005$). LVDd was larger in PA cases than in non-PA cases, but the difference was not significant ($P=0.15$).

eight induced-abortion cases, %FS ranged from 10 to 22% and was unchanged at 20 months after abortion. LVDd did not differ significantly between the good and poor prognosis groups (Figure 2), but was significantly elongated at the initial examination during pregnancy in two patients who subsequently died. In an receiver operating characteristic analysis of the relationship of the %FS value to poor maternal prognosis, the area under the curve (AUC) was 0.9778 and the value of %FS that showed the best sensitivity (one specificity) was 20.5.

Table 2 Outcome of pregnancy and cardiac function

Heart failure[a]	*PA (n = 14)*		*Non-PA (n = 15)*	
	Yes (6)	*No (8)*	*Yes (0)*	*No (15)*
Delivered cases	6	4	—	11
%FS (%)[b]	17.0 ± 3.1	25.6 ± 1.6	—	28.1 ± 4.0
LVDd (mm)	60.0 ± 8.5	55.5 ± 1.9	—	53.7 ± 3.8
Delivery weeks[c]	32.4 ± 3.2	36.4 ± 2.8	—	37.8 ± 1.0
Birth weight (g)[c]	1952 ± 585	2436 ± 500	—	2815 ± 352
Delivery mode				
Vaginal	3	2	—	6
Cesarean section	3	2	—	5
Fetus				
IUGR	0	0	—	0
IUFD	2	0	—	0

Abbreviations: PA, pregnancy associated (DCM occurred in the first 7 months of pregnancy); non-PA, non-pregnancy associated (DCM occurred before pregnancy); %FS, percent fractional shortening; LVDd, left ventricle end-diastolic dimension; IUGR, intrauterine growth retardation; IUFD, intrauterine fetal death.
[a]Incidence of heart failure was significantly higher in PA cases than in non-PA cases (6/14 versus 0/15, $P<0.005$).
[b]%FS was lower in six heart failure cases than in PA cases without heart failure (17.0 versus 25.6%, $P<0.005$) and in non-PA cases (17.0 versus 28.1%, $P<0.001$).
[c]Week of delivery and birth weight of newborns were both lower in heart failure cases than in PA cases without heart failure (32.4 versus 36.4 weeks, $P<0.01$; 1952 versus 2436 g, $P<0.01$) and in non-PA cases (32.4 versus 37.8 weeks, $P<0.01$; 1952 versus 2815 g, $P<0.01$).

Changes in NYHA class

In the 21 delivery cases, all the non-PA patients remained in NYHA class I throughout the observed course (Figure 3). Of the 10 PA delivery cases, 9 were in NYHA class I early in pregnancy. However, the NYHA class worsened as pregnancy progressed, except in one case, three patients died due to severe heart failure, three were in class II and three were in class III or IV with severe heart failure. All of the eight abortion cases had maintained the same NYHA class (six in class I, two in class II) at 20 months after abortion.

Discussion

The analysis of risk factors for maternal outcome in patients with DCM-complicated pregnancy showed that a low %FS and onset of DCM during pregnancy increased the risk of heart failure at 1 year after delivery.

Left ventricular fractional shortening

LV %FS and LVDd are predictive factors for poor prognosis in DCM among non-pregnant patients.[17,18] Our cases with decreased LV function are clearly distinguishable from PPCM, as patients with cardiac dysfunction that developed early in pregnancy are included in our study, whereas such cases are generally excluded from a PPCM cohort. Low cardiac function at the time of diagnosis of PPCM is a predictive factor for mortality.[3,19–22] Witlin *et al.*[23] reported that six of seven patients with severe PPCM

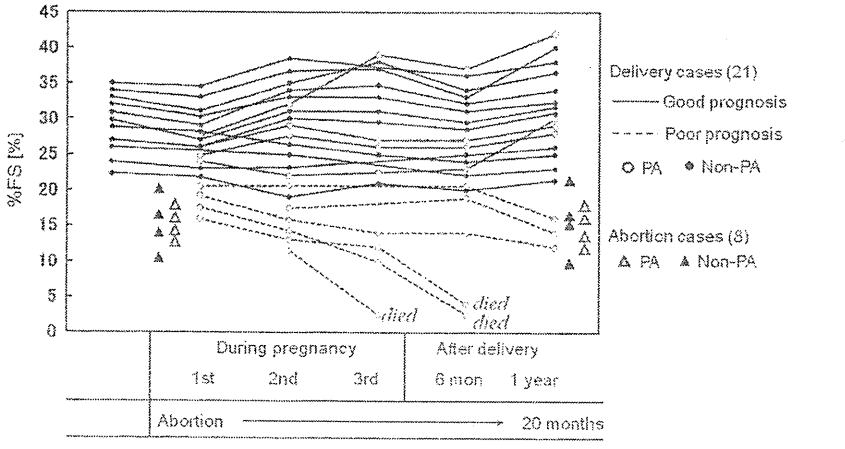

Figure 1 Longitudinal changes of fractional shortening (%FS). Most cases with a good prognosis (full line) had a higher %FS than cases with a poor prognosis (dotted line). In abortion cases, %FS ranged from 10 to 22% when abortion was induced and these values had not changed at 20 months after abortion.
PA, pregnancy associated; non-PA, non-pregnancy associated.