Table 16. Important Adverse Drug Reactions to Tocolytics

Ritodrine (β-stimulant)	
Significant ADRs:	Pulmonary edema, acute heart failure, agranulocytosis, hypokalemia, rhabdomyolysis
Neonates:	Ventricular septal thickening, intestinal obstruction
Others:	Tachycardia, arrhythmia (mother and fetus), hepatic dysfunction, thrombocytopenia, tremor, hyperglycemia, salivary gland swelling associated with hyperamylasemia, headache, erythema
Magnesium sulfate	
Significant ADRs:	Pulmonary edema, respiratory failure, heart block, cardiac arrest, tetany, muscular paralysis, hypoglycemia, facial flashing, hot flash, paralytic ileus, rhabdomyolysis
Neonates:	Abnormal bone findings (transverse radiolucent bands and thin skin proximal humeral diaphysis)
Indomethacin (not indicated in Japan)	
Significant ADRs:	Shock, hepatic dysfunction, renal failure, gastrointestinal bleeding, asthma, aplastic anemia, hemolytic anemia, mucocutaneous ocular syndrome (Stevens-Johnson syndrome), oligohydramnios
Fetuses:	Ductus contraction, renal failure, bowel perforation
Neonates:	Necrotizing enterocolitis

ADR, adverse drug reaction.

Table 17. Indications for Cesarean Section

General conditions

1) Maternal indications

- Cephalopelvic disproportion
- Pelvic soft tissue stiffness
- Difficulty with vaginal delivery due to stenosis, scarring, or pelvic tumors
- When a risk of uterine rupture is present (women who had underwent cesarean section and women with a history of enucleatic myomectomy)
- When the mother is at a risk (eg, complicated with severe pregnancy-induced hypertension, eclampsia, placenta previa, premature separation of the normally implanted placenta, heart disease, lung disease, renal disease and liver disease)
- When vaginal delivery through trial labor, vacuum extraction and forceps delivery is not expected successful

2) Fetal indications

- Non-reassuring fetal status
- Umbilical cord prolapse
- Unreduced transverse presentation, abnormal position, malpresentation or abnormal rotation of the fetus
- Pelvic presentation suggesting fetal immaturity

Maternal heart disease

- Cardiac dysfunction
- Patients at a risk of unstable hemodynamics induced by changes in blood pressure, for example patients with Marfan syndrome, significant coarctation of the aorta, aortic stenosis or severe pulmonary artery stenosis, and patients following Fontan operation (vaginal delivery is possible in only limited cases)
- Pulmonary hypertension
- Uncontrolled arrhythmia
- Patients using mechanical valves
- Patients with cyanosis

Table 18. Considerations in Selection of Anesthetic Methods During Cesarean Section in Patients With Heart Disease

	Spinal (subarachnoid) anesthesia	Epidural anesthesia	General anesthesia
Risk of aspiration pneumonitis	Almost absent	Almost absent	Present
Sympatholytic action	Rapid	Slow	Slight
Sympathetic stimulant	Absent	Absent	During intubation/extubation
Systemic vascular resistance	Decrease	Decrease	Increase during light anesthesia Decrease by anesthetic agents
Pulmonary vascular resistance	Difficult to control	Difficult to control	Controllable through mechanical ventilation
Intrathoracic pressure	Not changed	Not changed	Increase by controlled ventilation
Cardiac contraction	Not changed	Not changed	Possible inhibition
Transesophageal echocardiography monitoring	Painful	Painful	Easy
Communications with staff	Possible	Possible	Impossible
Use during anticoagulation therapy	Avoid	Avoid	Low risk

Table 13. Underlying Heart Disease and Anesthetic Methods

Diagnosis	Vaginal delivery				Cesarean section				
	No	Spinal	Epidural	Sedation	Spinal	Epidural	CSEA	General	Other
• Arrhythmias									
Tachyarrhythmia									
Tachycardia									
Supraventricular tachycardia	○		◎		●		●	◎	
Ventricular tachycardia	◎		◎		○			◎	
Congenital long QT syndrome			●	○	◎	●	◎	◎	
Arrhythmogenic right ventricular dysplasia	○		○			●			
Fibrillation and flutter									
Atrial fibrillation			◎					○	
Preexcitation syndrome									
WPW syndrome	◎	●	◎		●			●	
Bradyarrhythmia									
Sinus bradycardia/sinus arrest	●								
Complete atrioventricular block	◎		●		○			●	
Artificial pacemaker	◎		●		○	●		●	
• Ischemic heart disease									
Angina			○ CSEA					●	
Acute myocardial infarction	◎					○		●	
Old myocardial infarction			●			◎		●	
Coronary arterial lesions due to Kawasaki disease			○			◎		◎	
• Congenital heart disease									
Eisenmenger syndrome	●				◎ CSA	●	●	◎	
Pulmonary stenosis		● CSA							
Congenital right pulmonary artery absent					○				
Tricuspid atresia					● CSA				
Fontan operation	●	○	●		● CSA	●		◎	
Ebstein anomary	○		●			●		◎	
Complete transposition of the great arteries						●		○	
Mustard operation	●					●		○	
Coarctation of the aorta	●		●			●	●	●	
Pulmonary valve atresia + ventricular sepal defect						●			
Pulmonary valve atresia + intact ventricular septum						●		●	
Corrected transposition of the great arteries			●		●	●		◎	
Double outlet right ventricle						◎	●	●	
Truncus arteriosus								●	
Coronary artery anomaly						●		●	
Single ventricle			●			●		●	
• Acquired valvular heart disease									
Mitral stenosis			◎			◎		◎	
Mitral regurgitation	●				○	●		○	
Aortic stenosis			●			◎		●	
Aortic regurgitation						○		●	
Mitral stenosis + aortic stenosis			●			●			
Mitral stenosis + aortic regurgitation								●	
Mitral regurgitation + aortic regurgitation			●						
Infective endocarditis	●				○			◎	
• Myocardial disease									
Cardiomyopathy									
Hypertrophic cardiomyopathy		○	◎			◎	○	◎	
Dilated cardiomyopathy	○		○			○	○	◎	
Peripartum cardiomyopathy	○		●			●	●	◎	Local infiltration
• Aortic disease									
Aortitis syndrome (Takayasu arteritis)			●			●	◎	●	
• Vascular lesions associated with congenital connective tissue disease									
Marfan syndrome			◎		○	◎	●	◎	
• Pulmonary heart disease									
Pulmonary arterial hypertension	●		●			◎	●	◎	

Note) ○ : reported only in Japan, ● : reported only in foreign countries, ◎ : reported in and outside of Japan.
CSA, continuous spinal anesthesia; CSEA, combined spinal epidural anesthesia; WPW, Wolff-Parkinson-White.

Table 20. Characteristics of Commonly Used Antiarrhythmic Drugs During Pregnancy and Lactation

Drug	V-W classification*1	Pregnancy categories*2	Indications	Characteristics/ adverse effects	Teratogenicity	Breast feeding	Package insert*3	
							Pregnancy	Lactation
Quinidine	IA	C	Various arrhythmias	Thrombocytopenia	Absent	Probably compatible	2	1
Procainamide	IA	C	Various arrhythmias	Lupus-like syndrome	Absent	Probably compatible	2	1
Disopyramide	IA	C	Various arrhythmias	Uterine contraction	Absent	Probably compatible	2	1
Lidocaine	IB	B	VT	Bradycardia, CNS adverse effects	Absent	Probably compatible	2	
Mexiletine	IB	C	VT	Bradycardia, CNS adverse effects, low birth weight infants	Absent	Probably compatible	2	1
Phenytoin	IB	D	Digitalis intoxication	Fetal hydantoin syndrome, not covered for arrhythmias	Present	Compatible	2	
Flecainide	IC	C	VT, SVT	No in normal heart	Absent	Probably compatible	1	1
Propafenone	IC	C	VT, SVT	No in normal heart	Absent	Probably compatible	2	1
Atenolol	II	D	SVT, VT, AF	IUGR, hypoglycemia, bradycardia	Absent	Potential toxicity	2	1
Propranolol	II	C→D	SVT, VT, AF	IUGR, hypoglycemia, bradycardia	Absent	Potential toxicity	2	1
Metoprolol	II	C→D	SVT, VT, AF	IUGR, hypoglycemia, bradycardia	Absent	Potential toxicity	1	1
Amiodarone	III	D	VT	Thyroid disorder, bradycardia, IUGR	Absent	Contraindicated	2	1
Sotalol	III	B→D	VT, SVT	Bradycardia	Absent	Potential toxicity	2	1
Verapamil	IV	C	SVT, VT, AF	Hypotension, bradycardia	Absent	Probably compatible	1	1
Adenosine	NA	C	SVT	Nausea, facial flushing	Absent	Probably compatible	2	
Digoxin	NA	C	SVT, AF	Bradycardia, low birth weight infants	Absent	Compatible	2	

AF, atrial fibrillation; CNS, central nervous system; IUGR, intrauterine growth retardation; NA, not applicable; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

*1Vaughan-Williams (V-W) classification of antiarrhythmic drugs. The above information is based on "Drugs in pregnancy and lactation, 8th edition (2008)".[49]

*2B→D/C→D: Pregnancy category B or C during the first trimester but pregnancy category D during the second and third trimesters.

*3Information on the use during pregnancy and lactation in the package insert (Blank columns represent no information in the source material).

1. Contraindication: This drug should not be administered to women who are or may be pregnant. Treatment should be discontinued without delay when pregnancy is detected. The drug should not be given to lactating women, and, when treatment is necessary, should be given after lactation is stopped.
2. Relative contraindication: The drug should be used when the benefits of use outweigh the risks. It is desirable that the treatment be avoided in women who are or may be pregnant. The safety in pregnant women has not been established.

[Precautions]

1) Indications and contraindications should be confirmed when considering the use during pregnancy.
2) When drugs contraindicated or not indicated for pregnant women in the package inserts, the physicians must fully explain the use of such drugs to the patients and their families and obtain informed consent.

to induce labor and patients with uterine inertia should be indicated for oxytocics.[109]

5. Delivery Methods

Vaginal delivery is generally recommended, although cesarean section is performed for selected cases (Table 17). Cesarean section is indicated for those with Marfan syndrome associated with an increase in ascending aortic diameter and those using artificial valves without hemostasis through switching from warfarin to heparin.[69] Cesarean section may be considered for other high-risk women. Epidural anesthesia is beneficial in reducing cardiac load by decreasing cardiac output, and in alleviating pain and anxiety of the patient.

6. Anesthesia for Delivery (Tables 18, 19)

Hemodynamics during delivery is significantly affected by the body position, delivery method, severity of labor pain, and depth of anesthesia. Epidural anesthesia is an excellent method to provide analgesic effect with limited effect on systemic hemodynamics.

Table 21. Characteristics of Drugs Commonly Used for the Treatment of Heart Failure During Pregnancy and Lactation

Drug	Class	Pregnancy categories*1	Characteristics/ adverse effects	Teratogenicity*1	Breast feeding	Package insert*2	
						Pregnancy	Lactation
Furosemide	Diuretic	C (D)	Decreased uteroplacental circulation, fetal dehydration	Absent	Probably compatible	2	1
Spironolactone	Diuretic	C (D)	Possible feminization	Absent	Probably compatible	2	1
Chlorothiazide	Diuretic	C (D)	Thrombocytopenia, hemolytic anemia	Absent	Compatible	2	1
Digoxin	Digitalis	C	Bradycardia, low birth weight infants	Absent	Compatible	2	
Nitroglycerin	Nitrate	B	Few reports	Absent	Probably compatible	2	1
Isosorbide dinitrate	Nitrate	C	Few reports	Absent	Probably compatible	2	1
Carvedilol	β-blocker	C→D	IUGR, bradycardia, hypoglycemia	Absent	Potential toxicity	1	1
Metoprolol	β-blocker	C→D	IUGR, bradycardia, hypoglycemia	Absent	Potential toxicity	1	1
Hydralazine	Peripheral vasodilator	C	Headache, neonatal thrombocytopenia	Absent	Probably compatible	2	1
Captopril*3	ACE inhibitor*3	C→D	Fetal renal dysplasia, renal failure, oligohydramnios	Present*3	Compatible	1	1
Enalapril*3	ACE inhibitor*3	C→D	Fetal renal dysplasia, renal failure, oligohydramnios	Present*3	Probably compatible	1	1
Candesartan*4 Losartan*4	Angiotensin receptor blocker*4	C→D	Fetal renal dysplasia, renal failure, oligohydramnios	Present*4	Probably compatible	1	1
Milrinone	PDE III inhibitor	C	Few reports	Absent	Probably compatible	2	1
Amrinone	PDE III inhibitor	C	Few reports	Absent	Probably compatible	1	1
Olprinone	PDE III inhibitor		Few reports			1	1
Carperitide	hANP		Few reports			2	1
Dopamine	Catecholamine	C	Few reports	Absent	Probably compatible	2	
Dobutamine	Catecholamine	B	Few reports	Absent	Probably compatible	2	
Isoproterenol	Catecholamine	C	Few reports	Absent	Probably compatible	2	

ACE, angiotensin converting enzyme; hANP, human atrial natriuretic peptide; IUGR, intrauterine growth retardation; PDE III, phosphodiesterase III.

Note) The above information is based on "Drugs in pregnancy and lactation, 8th edition (2008)"[43] (Blank columns represent no information in the source material).

*1C→D: Pregnancy category C during the first trimester but pregnancy category D during the second and third trimesters. C (D): Pregnancy category C for patients without gestational hypertension, and pregnancy category D for patients with gestational hypertension. Teratogenicity: Since ACE inhibitors have been reported to be teratogenic, strict caution should be needed for the use of these drugs even in the first trimester.

*2Information on the use during pregnancy and lactation in the package insert (Blank columns represent no information in the source material).

1. Contraindication: This drug should not be administered to women who are or may be pregnant. Treatment should be discontinued without delay when pregnancy is detected. The drug should not be given to lactating women, and, when treatment is necessary, should be given after lactation is stopped.
2. Relative contraindication: The drug should be used when the benefits of use outweigh the risks. It is desirable that the treatment be avoided in women who are or may be pregnant.

*3Since ACE inhibitors have been reported to be teratogenic, strict caution should be needed for the use of these drugs even in the first trimester.

*4Strict caution in terms of teratogenicity should be needed for the use of angiotensin receptor blockers, which exert their effects in a way similar to ACE inhibitors.

[Precautions]

1) Indications and contraindications should be confirmed when considering the use during pregnancy.
2) When drugs contraindicated or not indicated for pregnant women in the package inserts, the physicians must fully explain the use of such drugs to the patients and their families and obtain informed consent.

Table 22. Directions of Future Research on Pregnancy and Childbirth in Patients With Heart Disease

1. Counseling	Management of pregnancy and delivery, hereditary (risk of familial recurrence), maternal and fetal prognosis, support by family, and psychological approaches
2. Organization	Team-based practice, criteria for desirable hospitals, and cooperation with perinatal medical centers
3. Maternal management	Hemodynamics monitoring, management corresponding to types of heart disease, contraceptions, drug therapy, cardiac intervention (catheter intervention, cardiovascular surgery), and paternal management
4. Fetal management	Effects of maternal heart disease on the fetus, effects of drug therapy in the mother on the fetus, monitoring of fetal well-being, diagnosis of congenital anomalies of the fetus, and fetal treatment
5. Perinatal management	Perinatal monitoring, induction of delivery, anesthetic methods, delivery management, neonatal management (premature birth, low birth weight infants, and infants with congenital heart disease), excretion of drugs to the mother in the milk, effects of lactation on maternal heart disease, and caring for baby
6. Long-term management for child and mother	Assessment of maternal cardiac function, effects of pregnancy and delivery on the natural history of heart disease, growth and development of the children, and precautions for next pregnancy

V Types and Key Points of Treatment of the Mother

1. Antiarrhythmic Treatment (Table 20)[110–112]

2. Heart Failure Treatment (Table 21)[113–116]

3. Invasive Treatment

It has been reported that intervention using balloon catheters during pregnancy is effective for patients with pulmonary stenosis, aortic stenosis or mitral stenosis.[117,118] Cardiovascular surgery during pregnancy is required in rare cases.[2,71] The appropriateness of cardiovascular surgery during pregnancy should be determined according to the progression of lesions in aortic stenosis; the worsening of valvular regurgitation or heart failure due to diseases associated with valvular regurgitation; the severity of aortic dissection or giant aneurisms in aortic dilatation, or the status of vegetation or worsening of heart failure in infective endocarditis, among other conditions.[119] When surgery during pregnancy is unavoidable, those performed at 16 to 20 weeks of gestation or 24 to 28 weeks of gestation or thereafter are safer to the fetus than in other periods. When surgery may be waited to 28 to 30 weeks of gestation or thereafter, surgery after childbirth may be feasible.[117,120]

VI Directions of Future Research (Table 22)

It is expected that team management of high-risk pregnant women will advance, the number of women with heart disease who become pregnant and have children will increase, and that patient registration systems will be operated more efficiently. We hope that the directions for future research will be delineated more clearly and many of current problems will be solved by the time of the next revision of the present guidelines.

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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) $\geq$48 mm and/or fractional shortening (%FS) $\leq$30% on echocardiography. Patients were followed until at least 1 year after delivery and were categorized into a poor prognosis group ($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 ($P<0.0005$). 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. *Journal of Perinatology* (2012) **32**, 170–175; doi:10.1038/jp.2011.81; published online 18 August 2011

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) $\geq$48 mm and/or fractional shortening (%FS) $\leq$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

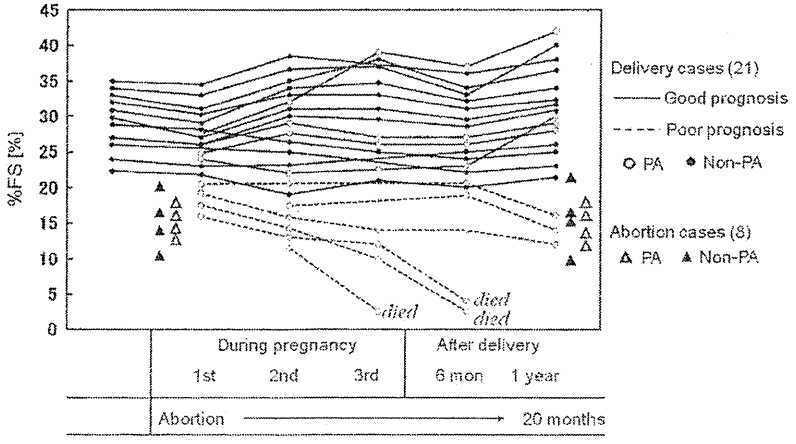

Figure 1 Longitudinal changes of fractional shortening (%FS). Most cases with a good prognosis (full line) had a higher %FS than cases with a poor prognosis (dotted line). In abortion cases, %FS ranged from 10 to 22% when abortion was induced and these values had not changed at 20 months after abortion.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

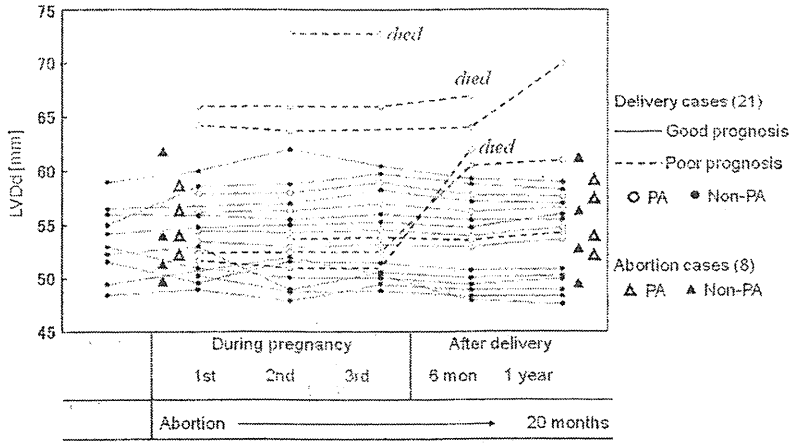

Figure 2 Longitudinal changes of left ventricle end-diastolic dimension (LVDd). In delivery cases, LVDd did not differ significantly between those with a good prognosis (full line) and a poor prognosis (dotted line). However, LVDd was significantly elongated in the initial test during pregnancy in two patients who subsequently died. PA, pregnancy associated; non-PA, non-pregnancy associated.

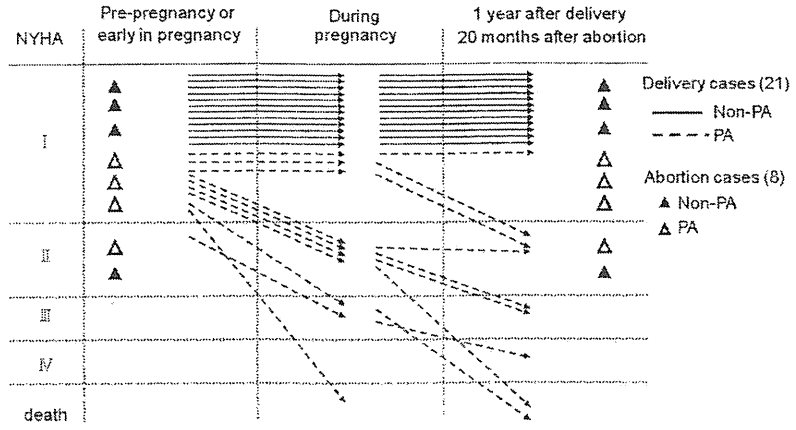

Figure 3 Changes of New York Heart Association (NYHA) class. All non-pregnancy associated (non-PA) cases (full line) and abortion cases maintained the same NYHA class throughout the study period. However, the NYHA class worsened as pregnancy progressed in most pregnancy associated (PA) cases (dotted line).

(LVDd $\geqslant$ 60 mm and %FS $\leqslant$ 21%) did not regain normal cardiac function in follow-up echocardiography and Chapa *et al.*[14] found that %FS <20%[24–26] and LVDd $\geqslant$ 60 mm at the time of diagnosis were associated with a more than three-fold risk for persistent LV dysfunction. In our patients, %FS <22% at the first test during pregnancy was predictive of worse cardiac function in late pregnancy and/or after delivery. In contrast, women who underwent abortion maintained cardiac function and NYHA functional class at 20 months after abortion. These results indicate that early termination of pregnancy prevents deterioration of cardiac function through avoidance of the stress and burden of pregnancy.

Pregnancy-associated DCM

Compared with women diagnosed with DCM before pregnancy, those diagnosed with DCM in early pregnancy had a higher incidence of heart failure and a poorer prognosis. In a comparison of maternal outcomes of 23 women with PPCM and 8 women with preexisting DCM, of the same age, Bernstein and Magriples[12] found that the outcomes of PPCM cases were significantly worse than those for preexisting DCM cases, with incidences of poor prognoses of 52 and 12%, respectively. Our patients are not comparable to the PPCM patients, as PPCM is defined as development of cardiac failure in the last month of pregnancy or within 5 months after delivery and thus has an acute clinical course.[19–21]

Early diagnosis and initiation of medication can lead to improvement of LV systolic function and the outcome of pregnancy.[19,20] In the non-PA group, seven patients received anti-cardiac remodeling therapy, with beta-blockers or diuretics before conception. This treatment may have led to the good maternal prognosis in this group. However, diagnosis of DCM and mildly decreased LV function in early pregnancy is very difficult if the

patient is free from symptoms, because echocardiography is seldom performed in early pregnancy in women with an apparently normal heart before pregnancy. We performed follow-up echocardiography when a pregnant woman complained of even mild fatigue, palpitation or dyspnea after DCM was diagnosed. However, such non-specific complaints are common in pregnant women without heart disease; therefore, patients with DCM and mild symptoms in early pregnancy may go unnoticed in routine medical examinations. Thus, some of our patients with mild to moderate dyspnea who were diagnosed with heart failure early in pregnancy might otherwise have been diagnosed with apparent heart failure late in pregnancy or after delivery. This assessment is consistent with the analysis by Elkayam *et al.*[3] of 123 women with cardiomyopathy diagnosed during pregnancy or in the postpartum period. That is, the clinical presentation and outcome of patients with PA cardiomyopathy diagnosed early in pregnancy are similar to those of patients with traditional PPCM. Therefore, these two conditions may represent a continuum of the same disease.

NYHA classification

The NYHA class I rating is used as the general standard for guidance of women with DCM, who want to become pregnant. In the current study, patients who had end stage heart failure or died late in pregnancy or after delivery were classified into NYHA class I in five cases and class II in one case in early pregnancy. These results indicate that NYHA class I is requisite for continuation of pregnancy, but cannot guarantee a good clinical outcome for mother and infant. Regardless of symptoms, echocardiographic findings of cardiac function (especially %FS) are necessary for prediction of the outcome of pregnancy.

Limitations

The patients with non-PA DCM performed better than the cohort with PA DCM. However, a selection bias may have been present, as we only studied patients who chose to pursue a pregnancy. Further, as our institution is a referral center for pregnancies with cardiovascular disease, some severe DCM cases that occurred during pregnancy were emergency maternal transfers to our center. These referrals may partly account for the worse cardiac performance and poorer maternal prognosis of patients with PA DCM, compared with those with non-PA DCM.

Conclusion

A low %FS (<22%) after conception and onset of DCM in early pregnancy are risk factors for a poor outcome in pregnancy complicated with DCM. Women who underwent abortion maintained cardiac function and NYHA functional classification over time, even though the %FS was low. The NYHA class in early pregnancy is not a predictor for maternal prognosis in women with DCM.

Conflict of interest

The authors declare no conflict of interest.

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心内膜心筋生検の役割
——二次性心筋症を中心として
Roles of endomyocardial biopsy

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◎心筋生検は，経皮的カテーテル検査時にバイオトームとよばれる小さな鉗子を用いて，患者の心臓内側から採取された大きさ2～3 mmのわずかな心筋組織について光学顕微鏡下で観察して病気の診断を行う病理検査である．心臓移植後の免疫抑制剤の効果判定や治療方針の決定に関して重要な役割を果たすとともに，心筋炎のほか，サルコイドーシス・Fabry病・アミロイドーシスなど，全身性疾患に伴う心疾患(二次性心筋症)を鑑別するなど，患者の治療方針の決定に重要な役割を果たしている．原因不明の心筋の病気である原発性心筋症(拡張型心筋症，肥大型心筋症，拘束型心筋症，不整脈源性右室心筋症)については，臨床所見と照らし合わせながら，これまでの経過も踏まえた診断や所見が重要となる．本稿では二次性心筋症を中心として，電子顕微鏡による超微形態を含めた形態学的特徴について述べる．

Key word　心筋炎，サルコイドーシス，アミロイドーシス，Fabry病，好酸球性心内膜心筋炎

心筋生検(心内膜心筋生検)は原因不明の心不全に対する診断過程の一環として行われる．心筋組織は心臓カテーテル検査時に，バイオトームとよばれる小さな生検鉗子を用いて，右室であれば心尖部中隔壁から採取される．組織学的に心筋細胞の肥大や変性，間質の線維化の程度なども評価されるが，生検組織は2～3 mm角と小さいため，病理組織診断の意義はおもに質的診断であるといえる．

心疾患には虚血性心疾患，高血圧性心疾患，弁膜疾患，先天性心疾患のほかに心筋自体に病因のある心筋症があり，心筋症は原因不明の原発性心筋症と全身性疾患の一部分症としての二次性心筋症とに分類される(表1)[1]．心筋生検は，なかでもとくに二次性心筋症の診断に大きな役割を果たしている．本稿では，当センターで経験したこれらの範疇に入る疾患を中心に述べたいと思う．

心筋生検が有用とされる疾患
1．心サルコイドーシス
サルコイドーシスは原因不明の全身性非乾酪性肉芽腫性疾患で，心臓にも病変が波及したサルコイドーシスを心サルコイドーシスという．肉眼的には，広くはっきりと輪郭された肉芽腫性炎症あるいは瘢痕の領域がみられる．好発部位は乳頭筋，心室中隔を含む心基部，伝導系，両心室の自由壁である．治療やその結果生じる線維化後，心室の自由壁に瘤が存在したり，心室中隔の上部が著明に菲薄化することがある．組織学的には心筋を置換する十分に形成された非壊死性肉芽腫が原則である．巨細胞は通常みられ，炎症部位が著明に広がり融合することがある．ステロイド療法を中心とする確立された治療方針から，心筋生検による診断的意義は大きい．とくに慢性心不全として加療され，高血圧性心疾患(HHD)あるいは拡張型心筋症の臨床診断のもと，心筋生検が施行された結果，非乾酪性肉芽腫を認める症例もときに経験される(図1)．

表 1　American Heart Association(AHA)から提唱された心筋症の分類(2006)

原発性心筋症	[遺伝性] 肥大型心筋症 不整脈源性右室心筋症 左室緻密化障害 Danon 病 伝導欠損(ラミノパチーなど) ミトコンドリア心筋症 イオンチャネル疾患 [混合] 拡張型心筋症 拘束型心筋症 [後天性] 炎症性心筋症 たこつぼ心筋症 産褥性心筋症 頻拍誘発性心筋症 幼児 IDDM
二次性心筋症	浸潤・沈着性(アミロイドーシスなど) 蓄積疾患(Fabry 病など) 心毒性(薬剤，化学物質など) 心内膜心筋性(Löeffler 心内膜炎など) 炎症性・肉芽腫性(サルコイドーシス) 内分泌性(糖尿病性など) 心・顔貌異常(Noonan 症候群など) 神経筋疾患(Duchenne-Becker 筋ジストロフィー，ネマリンミオパチーなど) 栄養障害 自己免疫性/膠原病 電解質異常 癌治療(抗癌剤，放射線など)

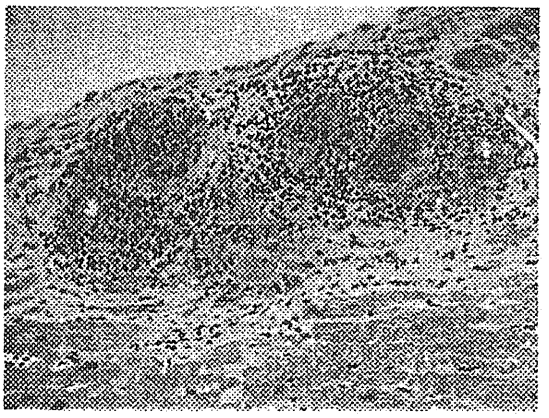

図 1　心サルコイドーシス例
H & E 染色，対物×20．心内膜に多核巨細胞を伴う非乾酪性肉芽腫が認められる．

一方，組織診断率は著者らの検討や報告でも20～30%前後と推定され，かならずしも全例において確定診断が可能なわけではない[2]．また，肉芽腫性心筋炎をきたす他の原因，とくにミコバクテリウムあるいは真菌感染を除外する必要がある．巨細胞性心筋炎との鑑別では，サルコイドーシスの場合では明らかな肉芽腫形成および典型的な大型の巨細胞を伴い，びまん性の心筋病変は比較的少なく線維化も優位である．

2. 急性および慢性心筋炎

特発性心筋炎の多くの例はウイルスが原因で起こる心筋炎と考えられ，結果として心筋細胞壊死および心筋の炎症が生じる．

肉眼的には，心筋は斑点状を呈する病変の有無にかかわらず，とくに著明な変化をきたさないものから柔らかいものまで多様である．壁在血栓の存在や心室の拡張がみられることがある．

組織学的には，リンパ球浸潤優位な心筋細胞壊死を特徴とするリンパ球性心筋炎であるが，炎症細胞は混在し巨細胞もときに出現する．大多数の症例では非特異的な心筋炎の変化を示す．ウイルス性心筋炎のもっとも一般的な原因は B 型コクサッキーウイルスであるが，単核球症やインフル

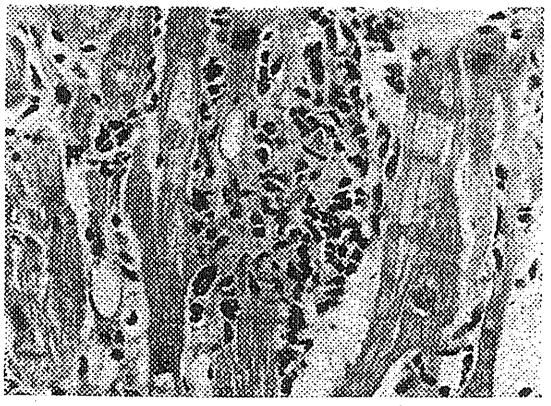

図 2　ステロイド療法が奏功した慢性心筋炎例
H & E 染色，対物×40．心筋内に限局性にリンパ球浸潤が認められ，心筋細胞傷害を伴う．

エンザを含む多くのウイルス疾患を伴う．また，流行期間中に生じたこのタイプの心筋炎は通常，流行性ウイルスに起因すると理解される．生検診断率について論じると，採取される心筋組織が3個の場合には5%，4個の場合で2%の偽陰性が生じると報告されている．急性心不全に至るような急性心筋炎であれば，病変はびまん性に及ぶため前述のような偽陰性率となるが，心筋細胞壊死や炎症細胞浸潤の病変が巣状で局所的な分布を呈する慢性心筋炎では(図2)，これより高い偽陰性を生じると推定される．しかし，慢性心不全や拡張型心筋症の臨床診断で生検された症例においても，巣状の心筋細胞壊死や炎症細胞浸潤が認められる例が存在しうる．従来の Dallas 分類では1回目の生検の場合，borderline myocarditis の範疇に入る病変であるが[3]，現在の WHF(World Heart Federation)分類では chronic myocarditis/DCMI (inflammatory dilated cardiomyopathy)に相当する病変である．間質へ浸潤する T リンパ球の数≧ 14/mm^{2}が盛り込まれているが，かならずしも厳格な規定ではなく，それよりも巣状の T リンパ球浸潤の有無が重要と考えられている．2回目の生検では Dallas 分類，WHO/WHF 分類ともに同じ用語が用いられている[4]．

慢性心筋炎の病因にはウイルス性，自己免疫性の両者が含まれるため，両者の鑑別には心筋組織を用いたウイルスのゲノム解析が必要であろう．しかし，ゲノムが存在しても，そのようなゲノムは活動性のある感染を示さないことがある．

3. 好酸球性心内膜心筋炎

原因にかかわらず，好酸球血症に伴う心筋炎の一型である．好酸球顆粒由来の陽荷電蛋白の傷害作用により明らかな心筋炎が二次的に生じる．蛋白は明らかな心筋細胞壊死を引き起こし，結果として種々の炎症細胞浸潤を伴う．なかには，好酸球の接着，脱顆粒に関連した心内膜傷害を伴って心内膜心筋炎が存在する．これはとくに右室流出路優位なことがある．晩期には心内膜心筋線維化がみられる．かならずしも好酸球増多症候群(hypereosinophilic syndrome：HES)を伴うとは限らず，末梢血の好酸球増多があっても心筋組織内に浸潤する好酸球数と parallel に相関するとは限らない．症例によっては全身の好酸球血症を伴わず，優位な好酸球浸潤を伴う壊死性心筋炎を呈し，急激に死に至る症例も存在する．慢性心筋炎や巨細胞性心筋炎でも好酸球浸潤を伴うが，高度な好酸球浸潤，好酸球浸潤を伴う心内膜炎の存在や好酸球を含む壁在血栓の有無などが診断の補助となる場合がある．

当センターでも，心筋梗塞類似の心電図変化を呈した成人例[5]や，拘束型心筋症(RCM)様の血行動態を呈した小児例において，好酸球性心内膜炎を呈した症例を経験している(図3-A)．ステロイド療法および抗凝固，抗血小板療法が施行された4週後の圧データは治療前と比較して肺動脈楔入圧は 18→10 mmHg，左室拡張末期圧は 19→13 mmHg，平均肺動脈圧は 34→17 mmHg と，それぞれ低下していた．また，同時に採取された心筋生検では心内膜の線維性肥厚が認められリンパ球が散見されたが，好酸球浸潤および壁在血栓は認められなかった(図3-B)．

4. アミロイドーシス

アミロイドーシスとは蛋白質を主成分とするアミロイドが種々の原因によって細胞外に沈着し，組織や臓器の機能異常を生じる疾患群である．アミロイドは形態学的にはヘマトキシリンエオジン染色でエオジンに淡染し，コンゴレッド染色で橙赤色に染まる．また，コンゴレッド染色標本を偏光顕微鏡下で観察するとアップルグリーンの複屈折を呈する．

全身性と限局性とに大別され，心血管領域で問

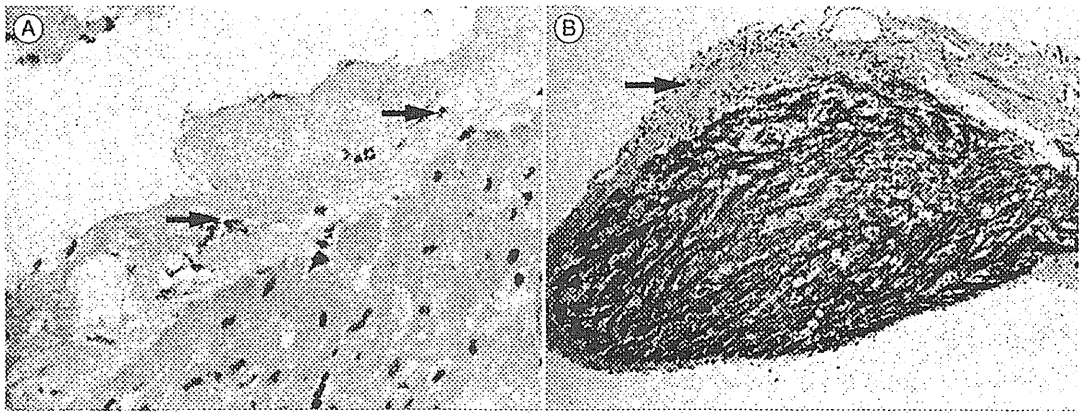

図 3　ステロイド療法が奏功した好酸球性心内膜炎例

A：H & E 染色，対物×40．心内膜に新鮮な壁在血栓を伴った好酸球浸潤(矢印)が認められる．

B：ステロイド療法後 1 カ月後の生検組織像．Masson trichrome，対物×4．心内膜には好酸球浸潤および壁在血栓がみられないが，線維性肥厚(矢印)が認められる．

題となるのは全身性アミロイドーシスのなかで，①免疫細胞性アミロイドーシス：AL(L 鎖 κ，λ)，AH(IgG1(γ1))，②反応性(続発性)アミロイドーシス(炎症，感染，結核，膠原病，悪性腫瘍)：AA(アポ SAA)，③家族性アミロイドポリニューロパチー(FAP)：ATTR(トランスサイレチン)，④透析アミロイドーシス：Aβ_2M(β_2 ミクログロブリン)，⑤老人性 TTR アミロイドーシス：ATTR(トランスサイレチン)と，限局性アミロイドーシスのなかで限局性心房性アミロイドーシス：AANF(心房ナトリウム利尿ペプチド)である．

肉眼的には硬く弾力性をもち，心房の心内膜は限局した顆粒状で，ロウのような外観を示す．心房は拡張し，心室は正常あるいは狭小化する．弁への沈着もロウのようで光沢をもつが，弁の機能は通常正常である．組織学的には，アミロイドは心房の厚い心内膜内，個々の心筋細胞周囲および巣状の沈着物として認められる．アミロイドの種類によって沈着様式に特徴があり，タイプを推定するのに有用である．間質パターンは ATTR と AL の 95%以上の症例で認められる．結節パターンは AL よりも ATTR において，心内膜および血管パターンは ATTR よりも AL において高頻度に認められる[6]．通常のコンゴレッド染色法では染色性が弱く，Puchtler ら[7]のアルカリコンゴレッド染色法が行われる場合があるが，この際，原法では媒染液および染色液に 1% NaOH を使用しており，この方法ではときに膠原線維や弾性線維の共染がみられる．膠原線維や弾性線維が共染すると，偏光顕微鏡下でわずかに緑色の複屈折を示し，アミロイドとの鑑別が困難になるので，注意が必要である．このため 1% NaOH の代りに 0.1% NaOH が推奨されている．また，確認のために電顕が必要なこともある．電顕上のアミロイド線維は分岐しないまっすぐな，あるいは曲がった構造で，不規則な配列を呈し，その径は 10 nm である(図 4)．アミロイド蛋白を同定するには，通常のホルマリン固定パラフィン切片を用いた免疫組織

図 4　アミロイドーシス例の電顕像

間質に 10 nm の径で分岐しない不規則な配列を呈するアミロイド線維が認められる．

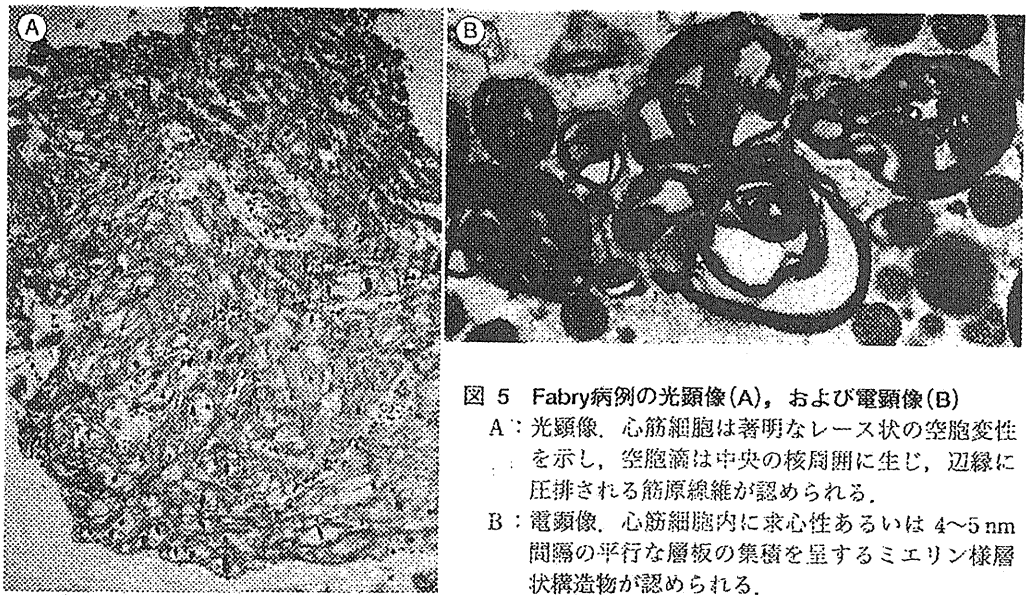

図 5　Fabry病例の光顕像(A)，および電顕像(B)
A：光顕像．心筋細胞は著明なレース状の空胞変性を示し，空胞滴は中央の核周囲に生じ，辺縁に圧排される筋原線維が認められる．
B：電顕像．心筋細胞内に求心性あるいは 4〜5 nm 間隔の平行な層板の集積を呈するミエリン様層状構造物が認められる．

化学的手法が有用である[8]．

5. Fabry病

Fabry 病は，水解小体のα-ガラクトシダーゼ A (セラミドトリヘキソシダーゼ)の欠損により全身にセラミドトリヘキソシドとよばれるグリコスフィンゴリピッドが蓄積する伴性劣性遺伝性疾患である．皮膚病変(被角血管腫)，疼痛，四肢の知覚異常，進行性の腎および心血管系疾患により特徴づけられる．心病変は皮膚病変に遅れて生じ，心拡大，うっ血性心不全，狭心症，高血圧を伴う．心臓の弁における病変も記載があり，僧帽弁狭窄および逆流，大動脈弁逆流，肺動脈弁逆流をきたす．本症は男性でより重症となり，ヘテロ接合体の女性はこれらのうちいくつかの症状を示す．肉眼的に心肥大は通常拡張を伴わない．しばしば肥大型心筋症と診断される[9,10]．巣状の線維化領域や心筋梗塞でさえ存在することがある．組織学的に心筋細胞は巣状の著明な空胞化を示し，刺激伝導系も侵されることがある．空胞滴は中央の核周囲に生じ，筋原線維は辺縁に圧排される(図 5-A)．凍結切片では空胞はズダン親和性，PAS 陽性で強い複屈折を示す．空胞滴は血管系全体を通して内皮細胞，平滑筋細胞，血管周囲細胞にみられ，とくに心筋内および心筋内の冠状動脈において顕著である．電顕上セラミドトリヘキソシドは，求心性あるいは 4〜5 nm 間隔の平行な層板の集積，いわゆるミエリン様層状構造物として形成しているのがみられる(図 5-B)．

表 2　心筋炎および二次性心筋症における心筋生検組織診断率

サルコイドーシス	34.6% (27/78)
心筋炎	60.3% (41/68)
アミロイドーシス	67.4% (23/34)
Fabry 病	75% (6/8)

おわりに

心筋生検には生検時の穿孔例もわずかではあるが認められ，サンプリングエラーの問題も存在するが，二次性心筋症の鑑別には重要な検査である．表 2 に当センターにおける心筋炎および上記二次性心筋症の心筋生検組織診断率を示す．病変がびまん性か限局性かによって診断率はさまざまである．このなかでは心筋炎，アミロイドーシス，Fabry 病のようなびまん性病変を呈しやすい疾患では組織診断率も高いためとくに有用と思われる．また近年では，高い空間分解能をもった遅延造影 MRI など画像検査の進歩に伴って，無症候性の梗塞像など微細な病変の把握が可能になりつつあり，信号の分布，形態，強度などから，できるかぎり病変の質的診断を行うことが望まれている．虚血や心筋炎以外に二次性心筋症の範疇に属する心疾患を，画像所見を含めたさまざまな臨床情報に基づいて鑑別し，正確な診断や病態を把握することは治療方針を決定するうえで重要である

ことから，今後，循環器疾患における病理の位置づけはますます重要になってくると思われる．

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