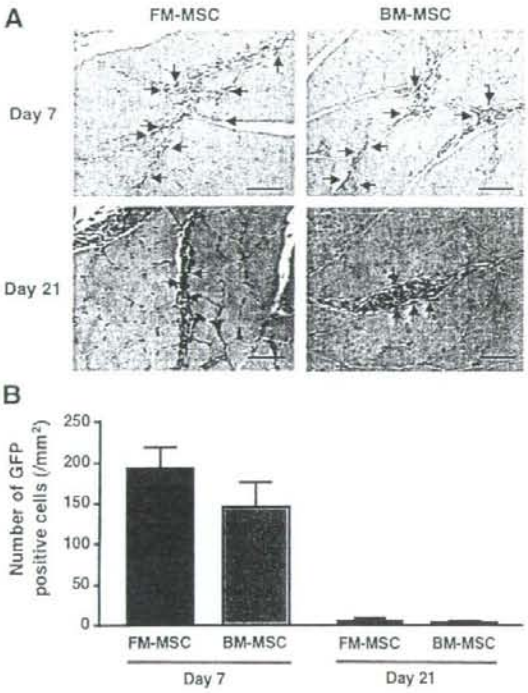

Figure 5. Engraftment of allogeneic FM-MSC and BM-MSC injected into ischemic hind limb muscles. **(A):** Representative sections show that GFP-positive allogeneic FM-MSC and BM-MSC were present in the hind limb muscles of rats with hind limb ischemia 1 and 3 weeks after cell injection (brown stain; black arrows). Scale bars = 50 μm. **(B):** Quantitative analysis demonstrated that comparable numbers of GFP-positive allogeneic FM-MSC and allogeneic BM-MSC were observed in ischemic hind limbs 1 week after cell injection. Three weeks after cell injection, a few GFP-positive allogeneic FM-MSC and BM-MSC were observed (n = 8 each). Data are mean ± SEM. Abbreviations: BM-MSC, bone marrow-derived mesenchymal stem cells; FM-MSC, fetal membrane mesenchymal stem cells; GFP, green fluorescent protein.

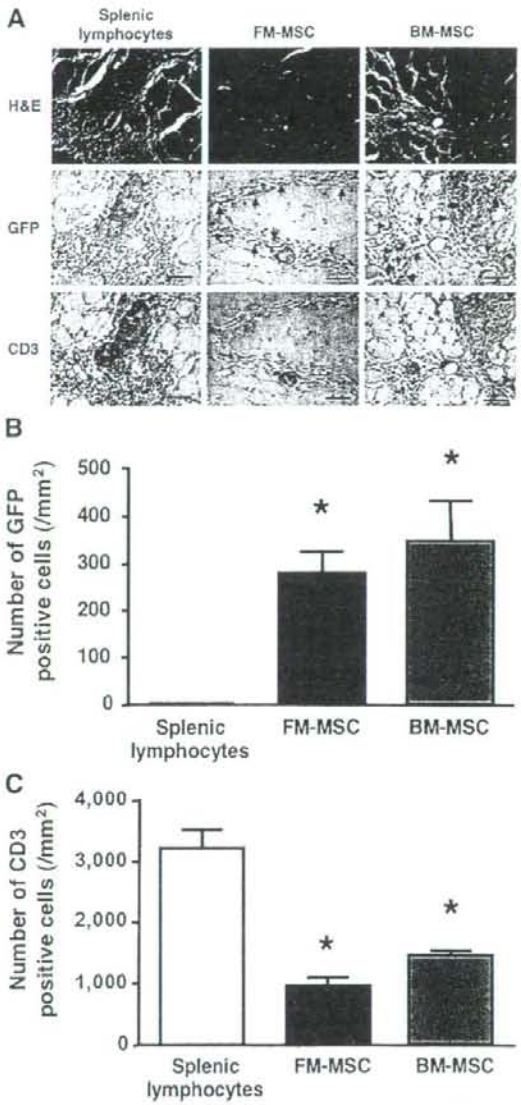

Figure 6. T lymphocyte alloreactivity after allogeneic FM-MSC and BM-MSC injection into hind limb muscles. **(A):** GFP-positive allogeneic FM-MSC and BM-MSC were observed 1 week after cell injection (brown stain; black arrows). T lymphocyte infiltration around injected allogeneic FM-MSC and BM-MSC was less marked than that around allogeneic splenic lymphocytes (brown stain). **(B):** Quantitative analysis of injected allogeneic GFP-positive FM-MSC and BM-MSC. The number of GFP-positive allogeneic FM-MSC was significantly higher than that of allogeneic splenic lymphocytes and equivalent to BM-MSC (n = 8 each). **(C):** Quantitative analysis of T lymphocyte infiltration at the site of allogeneic cell injection. The number of CD3-positive cells around injected allogeneic FM-MSC was significantly lower than that around allogeneic splenic lymphocytes and equivalent to BM-MSC (n = 8 each). Data are mean ± SEM. *, $p < .05$ versus splenic lymphocytes. Scale bars = 50 μm. Abbreviations: BM-MSC, bone marrow-derived mesenchymal stem cells; FM-MSC, fetal membrane mesenchymal stem cells; GFP, green fluorescent protein.

clinical and clinical studies, allogeneic MSC were not rejected and showed long-term engraftment in a variety of tissues in the absence of immunosuppression [32–34]. In the present study, FM-MSC had an immunophenotype similar to that of BM-MSC and did not provoke alloreactive lymphocyte proliferation in MLC. In normal rats, T lymphocyte infiltration was observed at the site of allogeneic FM-MSC injection; however, the degree of infiltration was less marked than that following allogeneic splenic lymphocyte injection and was equivalent to that induced by allogeneic BM-MSC. These results suggest that FM-MSC and BM-MSC can both evade T lymphocyte alloreactivity and may be successfully transplanted across MHC barriers.

In this study, we have reported for the first time the angiogenic effects of allogeneic FM-MSC. Some earlier studies have reported that grafted cells directly contributed to vessels and tissues in ischemic models [35, 36]. However, in our study, immunostaining of more than 30 sections of ischemic tissue revealed no evidence of endothelial differentiation or cellular fusion of transplanted FM- or BM-MSC (supplemental online Fig. 1). Recent studies have demonstrated that a direct contribution of grafted cells is minimal or even absent [37–39] and that paracrine actions are of major importance in mediating their regenerative effects [40, 41]. We also demonstrated that allogeneic injection of FM-MSC, as well as BM-MSC, significantly

increased blood perfusion and capillary density in rats with hind limb ischemia.

Recently, MSC have been considered to induce neovascularization by secreting large amounts of humoral factors involved in angiogenesis [42–45]. Our previous studies found that BM-MSC secreted large amounts of VEGF and HGF, which are known potent angiogenic factors [21, 27]. In this study, we showed that cultured FM-MSC secreted a comparable amount of HGF, but less VEGF, compared with BM-MSC. In our recent unpublished study, angiogenic gene polymerase chain reaction array analysis demonstrated that FM-MSC, as well as BM-MSC, expressed significant amounts of other angiogenesis-related genes, including VEGF-C, platelet-derived growth factor-B, angiopoietins, chemokines, and interleukins (data not shown). Our observation that FM-MSC and BM-MSC injection equally recovered blood perfusion of ischemic hind limb indicates that the angiogenic effect of FM-MSC, as a source of "cytokine cocktails," was equivalent to that of BM-MSC. There is another possibility that FM- and BM-MSC might have mobilized host stem/progenitor cells (e.g., endothelial progenitor cells) to the injured site to accelerate angiogenesis [46, 47].

We demonstrated that injected allogeneic FM- and BM-MSC were able to survive in the ischemic hind limb tissue 3 weeks after injection, although the cell number significantly decreased. A previous report found that transplanted allogeneic BM-MSC were observed 6 months after transplantation [32]. However, as in other studies, allogeneic MSC engraftment rates decreased with time [34, 48, 49]. Additional studies on the relationship between cell survivability and angiogenic effects are needed.

FM are a potentially promising cell source for clinical use; they are medical waste material, are abundantly available from maternity wards, and are free from ethical concerns. A further advantage of FM is that no invasive procedures are required to obtain MSC, unlike BM. Recently, MSC derived from cord blood have been demonstrated to be an attractive therapeutic cell source [50]. FM seem to be an another suitable alternative source of fetal-derived MSC for regenerative medicine.

Conclusion

FM-MSC did not elicit alloreactive lymphocyte proliferation, and allogeneic injection of FM-MSC induced therapeutic angiogenesis in a rat model of hind limb ischemia, comparable to that seen with BM-MSC injection. Considering that FM are generally treated as medical waste and that MSC can be obtained abundantly without invasive procedures, allogeneic FM-MSC injection could provide a new therapeutic strategy for the treatment of severe peripheral vascular disease.

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Disclosure of Potential Conflicts of Interest

The authors indicate no potential conflicts of interest.

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Review Article

Role of Echocardiography in Assessing Pregnant Women With and Without Heart Disease

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Abstract

The cardiocirculatory changes during pregnancy and delivery are marked. In some diseases and conditions, the maternal and fetal risks are high. Echocardiography plays a very important role to diagnose and to follow up in pregnant women with heart diseases, because it is noninvasive and does not expose the patients to radiation. We reviewed the value of echocardiography to determine the conditions under which women with heart disease can tolerate pregnancy, and the fetomaternal prognosis for major heart diseases.

(J Echocardiogr 2008; 6: 29-38)

Key words: pregnancy, heart disease, echocardiography, fetomaternal prognosis

Introduction

With recent advances in cardiovascular and neonatal medicine, the number of patients with heart disease who reach childbearing age has increased, and the range and severity of heart diseases with which pregnancy and delivery are possible is expanding. Subsequently, guidelines have been prepared in various countries[1, 2]. In Japan, the Japanese Circulation Society (JCS) joint working group issued guidelines for the management of pregnancy and delivery in women with heart diseases in 2005 (JCS 2005 guidelines)[3]. The cardiocirculatory changes associated with pregnancy and delivery are marked, and in some diseases and conditions, the maternal and fetal risks are high. In this review article, we emphasized the value of echocardiography to (1) examine healthy pregnant women, (2) determine the conditions under which women with heart disease can tolerate pregnancy, and (3) determine the fetomaternal prognosis for major heart diseases.

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1. Echocardiographic findings and hemodynamic changes during pregnancy in healthy pregnant women

Echocardiography can assess the hemodynamic changes noninvasively, thus it is widely used to measure cardiocirculatory indexes during pregnancy and after delivery.

From the sixth week of gestation to the second trimester during pregnancy, through the mechanisms such as water and sodium retention mediated by the renin-aldosterone system stimulated by the estrogen increase, the volume of circulating plasma is increased by an average of 1.5 fold. Cardiac output measured by Doppler echocardiography also increases by approximately 50 percent. From weeks 20 to 24, stroke volume increases reaching its peak, and then heart rate increases by 10 to 20 beats/min (Figure 1)[4]. On the other hand, arterial pressure and systemic vascular resistance decrease[5].

During labor and delivery, oxygen consumption increases about three fold, and uterine contraction

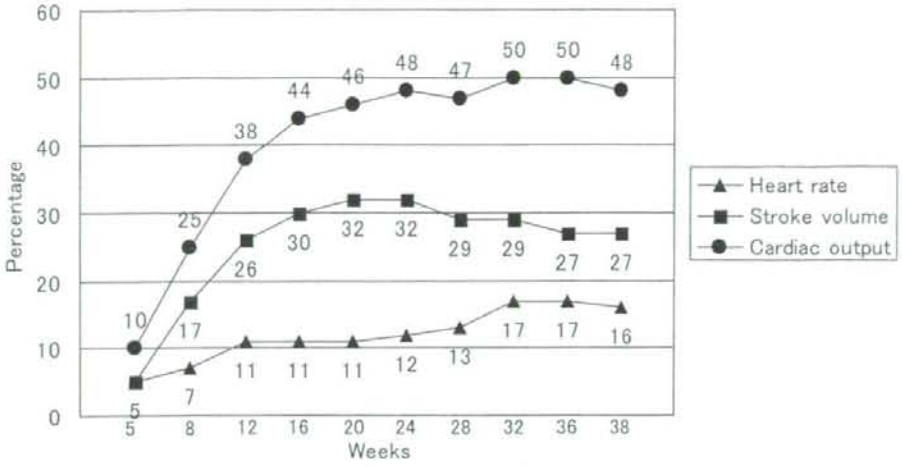

Fig. 1. Percent changes in heart rate, stroke volume, and cardiac output measured by echocardiography in the lateral position throughout pregnancy[4] (modified by and taken from the textbook "Braunwald's heart disease 7th edition, p1966")

accompanying labor increases the amount of circulating blood by 300-500 ml. At the same time, cardiac output increases by 15-25%, exceeding 8-10 L/min. Immediately after delivery, uterus-induced compression of the inferior vena cava is relieved, thereby rapidly elevating venous return. Cardiac output decreases by 10-20% within one hour of delivery. As the amount of circulating blood increases during pregnancy, transient overload persists for 4 to 6 weeks after delivery[6].

With regard to the changes in echocardiographic parameters, left ventricular (LV) end-diastolic and end-systolic dimensions and wall thickness increase, and contractile function enhances. Functional pulmonary, tricuspid and mitral regurgitation, and mild pericardial effusion are occasionally seen in normal pregnancy. About diastolic performance, findings such as significant increases in transmitral peak E velocity in the first trimester and peak A velocity in the third trimester of pregnancy have been reported[7]. Tissue Doppler echocardiography determined mitral annular early diastolic velocity (E') decreases, and late diastolic velocity (A') remains unaltered [8].

2. Required conditions for pregnancy based on echocardiographic findings

We have experienced about 70 deliveries of heart disease women over one year. Figure 2 shows the annual number of deliveries by women with heart disease in our hospital. While the number of patients with arrhythmia is almost constant, those with congenital heart disease or other heart diseases tend to increase.

In the past, medical decisions as to whether heart disease patients could become pregnant and deliver were based on the heart function classification system developed by the New York Heart Association (NYHA), and it has been generally accepted that class I or II women can become pregnant. Studies have shown that the maternal mortality for NYHA class I/II was <1% and for NYHA class III/IV was 5-15%[9], and the rate of maternal cardiovascular events such as heart failure, arrhythmia and cerebral infarction for NYHA class I was about 10% and for II/III/IV was about 30%. The rate of live-born infants for NYHA class I was about 80% and for II/III/IV was about 70%[10].

Recently, echocardiographic parameters have been widely used to determine the risk of pregnancy. A study of 562 pregnant women with heart diseases identified the following factors for poor maternal prognosis: prior cardiac event (heart failure, transient ischemic attack, or stroke before pregnancy) or arrhythmia, NYHA functional class > II or cyanosis, left heart obstruction (mitral valve area < 2 cm^2, aortic valve area < 1.5 cm^2, or peak left ventricular outflow tract gradient > 30mmHg by echocardiography) and systemic ventricular dysfunction (ejection fraction < 40%). When assigning one point for each condition, the incidence of maternal cardiovascular events during pregnancy was

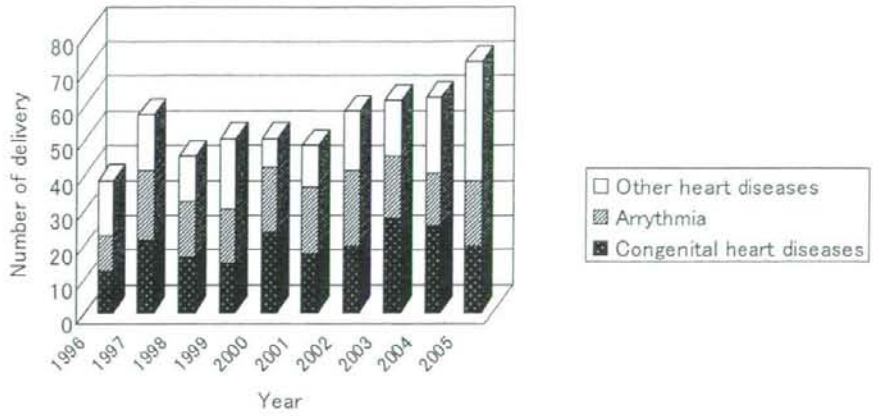

Fig. 2. The annual number of deliveries by women with heart disease at National Cardiovascular Center

Table 1. Multivariate analyses of maternal and neonatal risk predictors

Complications	Predictor	Odds Ratio (95% CI)	P
Cardiac	Prior cardiac event or arrhythmia	6 (3-14)	< 0.001
	NYHA functional class > II or cyanosis	6 (2-22)	0.009
	Left heart obstruction	6 (3-14)	< 0.001
	Systemic ventricular dysfunction	11 (4-34)	< 0.001
Neonatal	NYHA functional class > II or cyanosis	3 (1.1-6.1)	0.035
	Heparin/warfarin during pregnancy	3 (1.4-8.2)	0.0093
	Smoking	2 (1.3-3.9)	0.0045
	Multiple gestation	22 (6-85)	< 0.001
	Left heart obstruction	2 (1.01-2.9)	0.044
Postpartum hemorrhage	Peripartum heparin or warfarin	7 (2-22)	0.001
	Cyanosis	27 (4-177)	< 0.001

CI : Confidence Interval, NYHA : New York Heart Association
(Modified by and taken from Siu : Circulation, 104 (5) [11])

5% for a score of 0 point, 27% for a score of 1 point and 75% for a score of 2 or higher. In addition, the incidence of fetal complications such as premature delivery and low birth weight reached 20%, and severe complications such as respiratory distress syndrome, intracranial bleeding and death were confirmed in 5%. The factors that exacerbated fetal prognosis were NYHA class > II or cyanotic heart disease, anticoagulant therapy, smoking, multiple pregnancy and left ventricular obstruction (Table 1) [11]. In addition to the above factors, a recent study documented other risk factors; severe pulmonary regurgitation and right ventricular dysfunction with an odds ratio of 9.0 and 27.2, respectively [12].

Based on these results, the JCS 2005 guidelines list heart diseases that require close monitoring during pregnancy or should avoid pregnancy (Table 2) [3]. Echocardiography plays a pivotal role in assessing these conditions.

Table 2. Heart diseases that require careful monitoring during pregnancy and diseases with which pregnancy should be avoided [3]

1. Pulmonary hypertension (Eisenmenger syndrome)
2. Outflow tract obstruction (severe aortic valve stenosis : >40-50 mmHg)
3. Heart failure (NYHA class: ≥ III, LVEF : <35-40%)
4. Marfan's syndrome (Diastolic aortic diameter : >40 mm)
5. Prosthetic valve
6. Cyanotic disease (oxygen saturation : <85%)

NYHA : New York Heart Association

3. Echocardiographic findings during pregnancy in cardiovascular diseases

Here, we describe major cardiovascular diseases in pregnancy with some case presentations.

3-1. Congenital heart disease

3-1-1. Non-cyanotic heart disease

Left-to-right shunts, such as atrial sepal defect (ASD), ventricular septal defect (VSD), patent foramen ovale (PFO), and patent ductus arteriosus (PDA) are sometimes diagnosed during pregnancy due to loud heart murmur from increased shunt volume caused by increased circulating blood volume (Figure 3). In patients with large shunt volume, decreases in peripheral vascular resistance balances out the increased blood volume, and in most cases, pregnancy and delivery are completed without any complications. However, caution must be exercised in the event of rapid bleeding, as peripheral vasoconstriction may increase shunt blood flow, decrease cardiac output and cause congestive heart failure, shock and ventricular fibrillation.

Masuda et al. reported changes in pulmonary output (Qp) and systemic output (Qs) measured by Doppler echocardiography in 17 pregnant women (10 with VSD and 7 with ASD) in our hospital. During pregnancy, both Qp and Qs increased in all patients, resulting in an insignificant change in Qp/Qs (Table 3) [13].

(1) ASD: When compared to normal pregnancy, the risks for miscarriage and premature birth are higher, and these conditions can accompany supraventricular arrhythmia or paradoxical emboli. One study found that when compared to pregnancy after ASD-closure surgery, pregnancy before surgery has higher risks for miscarriage and maternal cardiovascular events[14]. Hence, if surgery is indicated, it should be performed before pregnancy. Recently, non-invasive procedure to close ASD was developed as an alternative treatment. There is a case report of percutaneous closure of ASD during pregnancy[15].

(2) VSD: In patients with untreated VSD without heart failure which is discovered during pregnancy, there are few problems, except when there is marked aortic regurgitation (AR) due to right coronary cusp herniation. As shunt volume of VSD is exaggerated by marked AR during pregnancy, surgery is recommended before pregnancy.

In a study of 309 pregnancies in 126 pregnant women with congenital heart diseases including ASD and VSD, the incidence of miscarriage was 17%, average duration of pregnancy was 34 weeks, maternal mortality was 0%, and fetal heart disease was 2.5%[16].

3-1-2. Non-cyanotic heart disease after surgical correction

In general, if patients keep good cardiac function, pregnancy and delivery are tolerable. Echocardiography often shows cardiac constrictive signs (such as septal bounce and increased respiratory changes in transmitral/transtricuspid flow) in pregnant patients who had open heart surgery. We think that increased blood volume can cause such a condition, and some should be carefully observed.

3-1-3. Cyanotic heart disease after surgical correction

In patients with good functional class (NYHA class I or II) and sinus rhythm, pregnancy and delivery are possible, but the incidence of miscarriage is high.

Repaired tetralogy of Fallot (TOF): In patients who underwent corrective surgery, pregnancy and delivery are possible. In one study of 112 pregnancies in 43

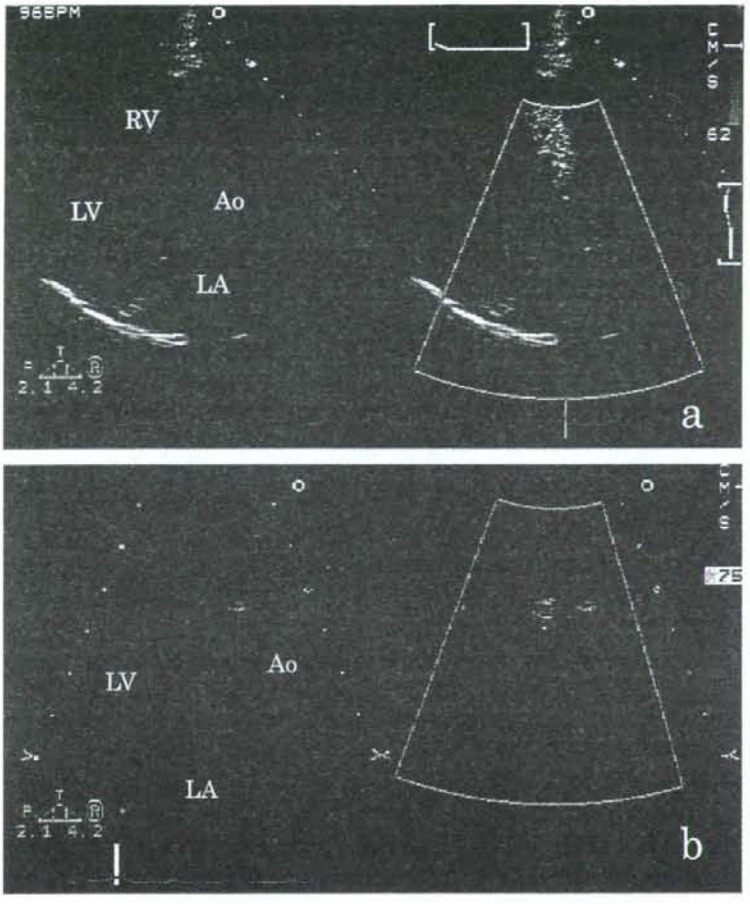

Fig. 3. Echocardiograms from a 29-year-old woman who was diagnosed with a small ventricular septal defect during her first pregnancy
Shunt flow increased in third trimester of her pregnancy (a) compared with 1 year after her delivery (b). Her left atrial dimension was 44mm during pregnancy. In contrast, it was 38mm after delivery.

Table 3. Changes in Qp/Qs measured by Doppler echocardiogram in 17 pregnant women with VSD or ASD

	Early phase of pregnancy (mean 13.8th week of gestation)	Early phase of pregnancy (mean 32.1th week of gestation)	Postpartum (mean 7.6 weeks after delivery)
Qp/Qs ratio in all patients (n=17)	1.78 ± 0.99	1.80 ± 0.76	1.56 ± 0.54
Qp/Qs ratio in VSD patients (n=10)	1.27 ± 0.17	1.52 ± 0.44	1.38 ± 0.38
Qp/Qs ratio in ASD patients (n=7)	2.50 ± 1.23	2.20 ± 0.96	1.88 ± 0.70

Qp; pulmonary output, Qs; systemic output, VSD; ventricular septal defect, ASD; atrial septal defect

patients of repaired TOF, delivery rate was 73%, and six women (14%) had cardiac events[17]. Pregnancy risk factors included: residual VSD, moderate to severe pulmonary valve stenosis and insufficiency, aortic insufficiency, pulmonary hypertension, dilated aorta (≥40 mm), ventricular dysfunction, and past history of tachyarrhythmia.

We experienced 14 deliveries in 13 patients of repaired TOF from 1998 to 2006. Three patients (23.1%) needed diuretics or bed rest because of pulmonary hypertension assessed by Doppler echocardiography.

3-1-4. Cyanotic heart disease without pulmonary hypertension

During pregnancy, systemic vascular resistance decreases to elevate right-to-left shunt, thus exacerbating cyanosis. While the incidence of complications is high in pregnant women with cyanotic heart diseases, cyanosis is treatable and mortality risk is low. However, fetal prognosis is poor, and in severe cyanosis, fetal development is hindered (the rate of live births is 12% at ≤85% oxygen saturation). In one study of 96 pregnancies in 44 patients with cyanotic heart diseases, maternal cardiac complications were seen in 32%, and the rate of live births was 43%. Hemoglobin≦ 16g/dL and oxygen saturation≦ 85% were found to be prognosticators[18].

3-2. Pulmonary hypertension

In patients with primary pulmonary hypertension, maternal mortality exceeds 50%, and pregnancy is contraindicated. In patients with Eisenmenger syndrome, maternal mortality ranges from 30 to 70%, and fetal mortality is as high as 50%[19, 20]. Hence, if patients with these diseases wish to continue their pregnancies, they must be admitted to a specialized hospital after week 20 of gestation to be treated with resting, oxygen administration and anticoagulation[21]. In our hospital, we experienced 2 (15.4%) maternal deaths among 13 patients with pulmonary hypertension[22].

Table 4. Maternal and fetal risk for patients with valvular disorders

	Low risk for mother and child	High risk for mother and child
Aortic stenosis	· Asymptomatic · Normal LV function · Mild to moderate stenosis : Systolic pressure gradient<40 ~50 mmHg	· Severe stenosis: systolic pressure gradient>40~50 mmHg · LV dysfunction
Aortic insufficiency	· NYHA class I/II · Normal LV function	· NYHA class III/IV · LV dysfunction
Mitral insufficiency	· NYHA class I/II · Normal LV function	· NYHA class III/IV · LV dysfunction
Mitral stenosis	· NYHA class I/II · Mild to moderate stenosis Valvular area:>1.5 cm^2 Pressure gradient:<5 mmHg · Without pulmonary hypertension	· NYHA class III/IV · Severe stenosis Valvular area:<1.5 cm^2 Pressure gradient:>5 mmHg · With pulmonary hypertension (≥75% systemic blood pressure)
High risks for mothers Left ventricular dysfunction (LVEF:<40%) Past history of heart failure Anticoagulation therapy during pregnancy (prosthetic valve patients) Past history of cerebral embolism or transient cerebral ischemia Aortic regurgitation accompanying Marfan's syndrome		
High risks for children Mother's age: <20 years or >35 years Anticoagulation therapy during pregnancy (prosthetic valve patients) Exposure to smoking, drinking or other environmental factors during pregnancy		

LV: left ventricular, NYHA: New York Heart Association, EF: ejection fraction
(Modified US ACC/AHA guidelines[25])

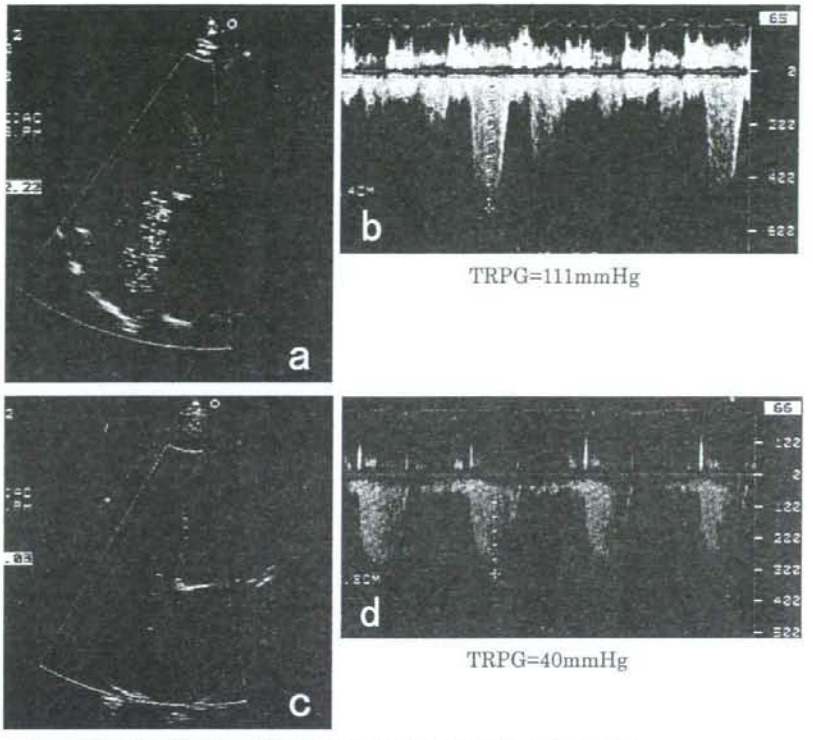

Fig. 4. Doppler echocardiograms from a woman with severe mitral stenosis
A thirty-one year-old woman with severe mitral stenosis (estimated mitral valve area= 0.6 cm^2) showed increased tricuspid regurgitation in her 26-week gestation (a) and decreased after cesarean section (c). The RA-RV pressure gradients derived by tricuspid regurgitant velocity (TRPG) also changed from 111 mmHg in her 26-week gestation (b) to 40 mmHg after cesarean section (d).

3-3. Patients with valvular disorders or prosthetic valves

During pregnancy, increased circulating blood volume often reduces cardiac function in patients with valvular heart diseases. The incidence of congestive heart failure and arrhythmia is about 40 and 15%, respectively, although maternal mortality is low[23]. Table 4 shows the JCS 2005 pregnancy guidelines for patients with valvular disorders established based on ACC/AHA guidelines[3, 24, 25].

Generally, patients with stenosis are less tolerable for volume overload than patients with regurgitation. We recommend patients with severe mitral or aortic stenosis to be treated by percutaneous transvenous mitral commissurotomy or operation before pregnancy. Figure 4 shows a 31 year-old woman with severe mitral stenosis who showed worsening pulmonary hypertension during her pregnancy and needed medical treatment and a cesarean section.

In patients with mechanical valves, because warfarin is teratogenic, heparin is used from weeks 6 to 12 of gestation, and then they are followed by subcutaneous low-molecular-weight heparin or oral warfarin with another switch to heparin at weeks 34 to 36. The risk for bleeding and embolization is high for both mothers and children. We reported pregnancy outcome in women with prosthetic mechanical valve replacement[26]. Among 16 pregnancies in 12 women with mechanical heart valve, 8 women (50%) had cesarean live births. Two babies died during the neonatal period. Four cases ended in early miscarriage, and one case ended in intrauterine fetal death. Therapeutic abortion was performed in 3 cases. Three mothers developed valve thrombosis, and one died from heart failure.

3-4. Marfan's syndrome

During pregnancy, estrogen and other hormones make vessels more fragile, and as a result, in pregnant

women with Marfan's syndrome, the risk for aortic dissection is higher than in non-pregnant women. In patients with annuloaortic ectasia (≥44 mm), pregnancy without replacement surgery is contraindicated. At 40-44 mm, while the risks are high, pregnancy and delivery are possible with conservative therapy although weekly echocardiographic observation is desirable. At <40 mm, normal delivery is possible. Under general anesthesia, cesarean section is performed, and blood pressure and pain management are very important.

We reviewed 8 pregnant patients with Marfan's syndrome experienced in our hospital[27]. Aortic dissection occurred in 3 patients (37.5%), one of whom developed rapid dilatation of the ascending aorta during her pregnancy and needed Bentall operation. Luckily, however, all patients tolerated the pregnancy well, with favorable maternal and fetal outcomes. Follow-up echocardiography showed no apparent worsening of cardiovascular status attributable to pregnancy except for one patient. In conclusion, dilatation of the ascending aorta during pregnancy is an important predictor for aortic dissection, and echocardiography must be performed weekly or biweekly.

3-5. Cardiomyopathy

Among pregnant women with hypertrophic cardiomyopathy, maternal mortality is around 1%, and most patients can go through pregnancy. However, in about half of the patients who had symptoms before pregnancy, the NYHA functional class was exacerbated (NYHA class III/IV) during pregnancy[28]. We often recognize elevated intraventricular pressure gradient and pulmonary hypertension in obstructive patients. Figure 5 shows a clinical course of a pregnant woman with hypertrophic obstructive cardiomyopathy. In patients at high risk for sudden death, such as those with ≥30 mm maximum wall thickness, past history of cardiac arrest or ventricular tachycardia and family history of sudden death, it is essential to carefully monitor pregnancy and delivery.

In dilated cardiomyopathy, because prognosis is poor, especially for young patients, and most patients take medication such as an ACE inhibitor, very few patients become pregnant. In general, maternal prognosis is also poor, and as a result, caution must be exercised, even in patients with mild cardiac dysfunction. In our hospital, in fact, we experienced 4 maternal deaths (death within 2 years after delivery) out of 8 patients with cardiomyopathy[22]. Figure 6 shows

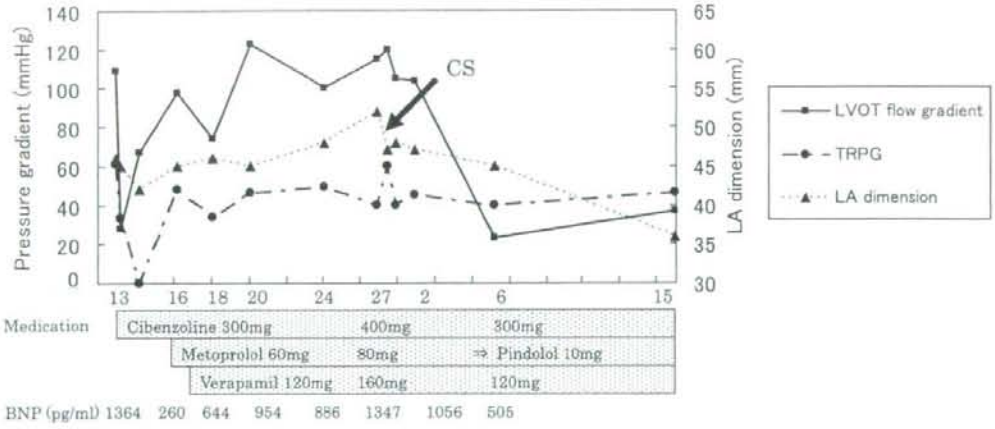

Fig. 5. The clinical course of a 30 year-old pregnant woman with hypertrophic obstructive cardiomyopathy
The patient was admitted during her 13th week of gestation. After she started to take cibenzoline, left ventricular outflow (LVOT) pressure gradient decreased from 109 mmHg to 28 mmHg and RA-RV pressure gradient derived by tricuspid regurgitant velocity (TRPG) also decreased. Then, the velocity gradually increased again, and additional medications were not effective to decrease it. At her 27th week of gestation, she started to complain of dyspnea on mild effort, and echocardiography showed increased left atrial (LA) dimension from 48 mm to 52 mm and increased mitral regurgitation from 2/4 to 3/4. She was taken for a cesarean section (CS) 3 days later. After delivery, LVOT pressure gradient decreased to around 30 mmHg.

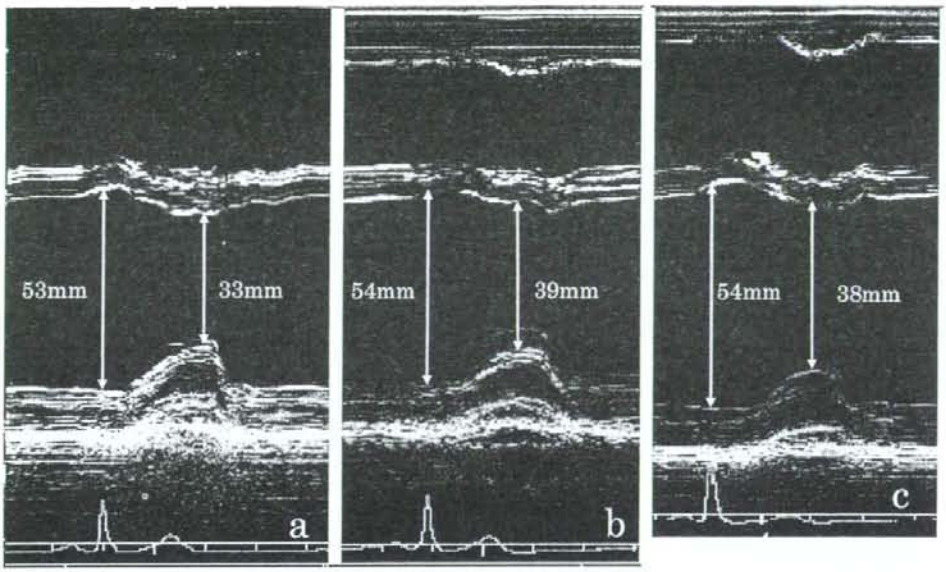

Fig. 6. M-mode echocardiographic changes in a woman with dilated cardiomyopathy (DCM) during her pregnancy and after delivery
The patient was a 26 year-old woman with slightly dilated left ventricle and history of ventricular tachyarrhythmia. At 16th week of gestation, left ventricular end-diastolic /end-systolic dimensions (LVDd/Ds) were 53/33 mm with fractional shortening (FS) of 37.7% (a) and at 36th week of gestation, LVDd/Ds were 54/39 mm (FS, 27.8%) (b). At 8 weeks after delivery, LVDd/Ds were 54/38 mm (FS, 29.6%) (c). Even in a mild DCM patient, peripartum left ventricular function is decreased.

changes in cardiac function during pregnancy and after delivery in a patient with dilated cardiomyopathy.

In peripartum cardiomyopathy, cardiac function recovers in about half of patients, but in this relatively rare disease, 20% of patients die or require a heart transplant. In patients with a past history of peripartum cardiomyopathy, multiple deliveries would worsen cardiac function, and as a result, caution must be exercised if a patient becomes pregnant again. The risk for cardiac events during first or subsequent pregnancy is dependent on the severity of left ventricular dysfunction[29], and assessment of left ventricular function by echocardiography is important.

4. Conclusions

In pregnant women with heart diseases, echocardiography plays a very important role because it is noninvasive and does not expose the patients to radiation. Long-term maternal prognosis has not been fully clarified, and there have been few studies investigating the relationship between echocardiographic findings and prognosis. Moreover, there are no reports about changes of cardiac function during pregnancy measured by new echocardiographic techniques such as tissue Doppler imaging and three-dimensional echocardiography[30, 31]. Further investigations are thus warranted.

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先天性心疾患と妊娠
－どこまで可能になったか－

池田 智明，根木 玲子

Abstract

Maternal Heart Disease and Pregnancy

Japan's maternal mortality rate is decreased, but during recent 10 years, it has not been decreased around 6 per 100000 live births. Further more, we assume the underreporting of pregnancy-related mortality in Japan. To solve this underreporting system, we tried to use the method of record linkage. We estimated maternal mortality in 2005 by using this method.

As a result, maternal mortality was estimated to be 1.35 fold more than officially reported, and maternal mortality rate increased from 5.7 to 7.4. (This statistics is permitted by The Ministry of Health, Labour and Welfare). Further more, indirect maternal death rate including maternal heart disease was much higher than direct maternal death rate. From this point of view, health statistics is thought to be underreported.

So, we focused on the pregnancy with heart disease. We investigated the risk factors which can be related to maternal mortality. We investigated retrospectively 1,387 pregnancies complicated with heart disease which have been managed in National Cardiovascular Center for past 26 years. Pregnancy with pulmonary hypertension (PH), dilated cardiomyopathy (DCM), Marfan syndrome is the high risk pregnancy which is highly related to maternal death. In these three heart diseases, the risk factors which can predict maternal mortality was investigated.

NYHA (New York Heart Association) class, pulmonary artery pressure by catheterization or echocardiography could predict the maternal death in pregnancy with PH. In pregnancy with DCM, decreased fractional shortening (FS) and peripartum onset could be a high risk factor. In Marfan syndrome, the risk factors of dissection of aorta during pregnancy are family history of sudden deaths or dissection of aorta. And an increased diameter of valsalva sinus (more than 40 mm) in early trimester of pregnancy is also a risk factor.

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Key words
maternal mortality,
maternal heart disease
brain natriuretic peptide (BNP)
congenital heart disease

国立循環器病センター 周産期科

はじめに(目的)

外科的手術を中心とした医療技術の向上により，先天性心疾患の修復術後の女性が，妊娠可能年齢に達したこと，また抗生剤の使用

により，リウマチ熱に起因する弁膜疾患の減少により，われわれ産婦人科医が遭遇する循環器疾患合併妊娠の種類も変化しつつある。先天性心疾患のなかでも，チアノーゼの残存，肺高血圧症の合併などは，母児のリスクが依然，残っている。また，人工弁置換術後妊娠の抗凝固療法による母児へのリスク，さらに，心筋症，心血管病変を伴うマルファン症候群など疾患そのものの重症度による母児へのリスクがあげられる。さらに，肺高血圧症や，心筋症，心血管病変を伴うマルファン症候群は，妊産婦死亡につながる心疾患として，英国の詳細な妊産婦調査によって挙げられており[1]，妊娠中は厳重な管理が必要である。

一方，わが国の妊産婦死亡に着目すると，近年減少傾向にはあるものの，諸外国の間接産科的死亡率や後発妊産婦死亡率と比較すると，日本の妊産婦死亡率は過少評価である可能性がある。この問題に対し，レコードリンケージという方法を用いて，平成17年における妊産婦死亡率を解析した結果，従来の人口動態統計よりも妊産婦死亡率は上昇することが判明した。なかでも，間接産科的死亡のうち，心疾患あるいは脳血管障害といった循環器病が原因の妊産婦死亡が上昇した[2]。

上記の疫学的データの結果を踏まえ，特に心疾患合併妊娠の妊産婦死亡につながるリスク因子について，国立循環器病センターで経験した症例について臨床的検討を行い，妊産婦死亡率を減少させる観点から，心疾患合併妊娠について解析を行った。

Ⅰ．方法および結果

1．ハイリスク妊娠―特に心疾患を中心に―の検討（国立循環器病センターで管理した心疾患合併妊娠）

前述のレコードリンケージ法において，間接産科的死亡の中でも，循環器疾患がクローズアップされた。そこで，循環器疾患のなかでも特に心疾患合併妊娠について，われわれの施設で取り扱った症例を中心に検討し，妊産婦死亡につながる，ハイリスク心疾患の抽出，さらに妊産婦死亡につながるリスク因子について解析を行った。

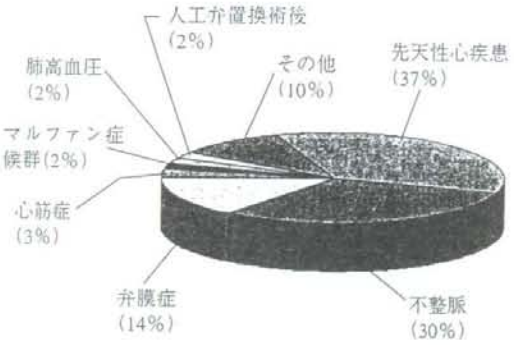

図1．1982～2007年に国立循環器病センターで管理した心疾患合併1,387例の内訳（総分娩数：5,606）

まず，過去26年間に，国立循環器病センターで管理した，心疾患合併妊娠，1,387妊娠の内訳を図1に示す。総分娩数は，5,606であり，約4分の1が心疾患合併妊娠であった。これら1,387例の心疾患合併妊娠について，以下の項目について検討した。

1）妊産婦死亡例，および妊娠中に人工心肺を必要とした症例についての検討

妊産婦死亡となった症例，ならびに妊娠中に人工心肺を必要としたハイリスク群を抽出，さらに妊産婦死亡につながるリスク因子について検討した。その結果，1,387妊娠の心臓病合併妊娠中，妊産婦死亡（分娩後1年までを含む）6例，妊娠中の人工心肺は5例であった。妊産婦死亡6例の内訳を表1に示す。原発性肺高血圧症（PPH：Primary Pulmonary Hypertension）1例，機械弁置換術後の1例，拡張型心筋症（DCM：Dilated Cardiomyopathy）の3例，完全房室ブロックの1例である。また，妊産婦死亡につながる，一歩手前の病態である，妊娠中に母体救命のために人工心肺を必要とした5症例の内訳を表2に示す。弁機能不

表1．心疾患合併妊娠における妊産婦死亡例
（1982-2007年，国立循環器病センター，分娩後1年以内）

心疾患名	年齢	経産	分娩週数	分娩様式	紹介～分娩	死亡時期	経過
1．原発性肺高血圧症	29	0	32週	帝切	2日	術中死亡	母体心不全による人工早産，麻酔導入時に母体心停止
2．大動脈弁置換後（機械弁）	35	0	30週	帝切	23日	3日	抗凝固薬を自己判断で中止．血栓形成のため，緊急で開心術
3．拡張型心筋症	24	1	34週	経膣	29日	5ヵ月	不整脈増加のため人工早産
4．拡張型心筋症	27	0	34週	帝切	2時間	3ヵ月	入院直後母体心不全（IUFD）
5．拡張型心筋症	33	4	27週	帝切	1時間	術中死亡	医療機関未受診，甲状腺腫合併（IUFD）
6．完全房室ブロック	36	1	39週	予定帝切	11日	2.5ヵ月	一時ペーシングリード挿入し帝切．分娩後2.5ヵ月でPulseless VF

表2．妊娠中に人工心肺の使用を必要とした症例
（1982～2007年，国立循環器病センター）

心疾患名	紹介前管理	入院週数	入院時症状	人工心肺使用週数	人工心肺使用適応	母体予後	児予後
1．大動脈弁置換（機械弁）	抗凝固療法なし	27週	動悸 呼吸困難	29週	弁機能不全（血栓弁）	母体死亡 術後3日目	胎児死亡 離脱時
2．僧帽弁置換後（生体弁）	妊娠7週から管理	20週	動悸	20週	弁機能不全	生存	胎児死亡 離脱時
3．マルファン症候群	妊娠初期に マルファンと診断	19週	無症状	19週	大動脈解離 78mm	生存	生存 37週
4．マルファン症候群	妊娠14週で， 大動脈拡大を指摘	15週	無症状	16週	大動脈解離 61mm	生存	生存 37週
5．肺高血圧症	正常妊婦として管理	30週	失神，喀血 呼吸困難	30週	右心不全	生存	生存 30週

全のため，再弁置換術を必要とした2例（妊娠29週，20週），マルファン症候群で大動脈解離の手術のため，人工心肺を必要とした2例（妊娠19週[3]，16週に施行），肺高血圧症（PH：Pulmonary Hypertension）1例，（PHによる右心不全進行のため，妊娠30週で経皮的人工心肺を施行，循環動態の安定を図りその後，帝王切開を施行）であった。妊産婦死亡例，妊娠中の人工心肺を必要としたいずれの症例も，紹介もしくは搬送日より短期間で分娩あるいは人工心肺を必要とした。また，妊産婦死亡の時期は，術中死亡の2例も含めると，いずれも産褥期の死亡であり，産褥期の管理が極めて重要であることが推察された。

そこで，ハイリスク心疾患として抽出された，PH，DCM，マルファン症候群合併妊娠の各疾患について，母体予後良好群および不良群に分けて，妊産婦死亡につながるリスク因子について解析した。

2）ハイリスク心疾患である①肺高血圧症（PH），②拡張型心筋症（DCM），③マルファン症候群における，妊産婦死亡につながるリスク因子の検討

表3．肺高血圧症における母体予後良好群および予後不良群の患者背景

	予後良好群 (Term) (n=9)	予後不良群 (Preterm) (n=16)
分娩時平均年齢(歳)	31.7	30.4
平均経妊回数	0.9	1.3
平均経産回数	0.4	0.3
帝王切開**	3/9	15/16
分娩週数(週)**	37.8	30.5
出生時体重(g)**	2,734	1,428
母体死亡	0/9	1/16
胎児・新生児死亡	0/9	2/16

**p<0.01

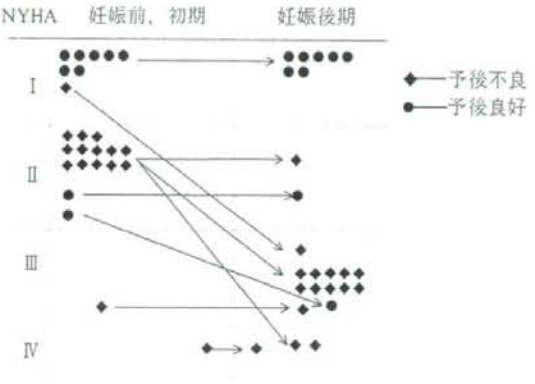

図2．肺高血圧症における妊娠中のNYHAの変化(n=25)

一般に妊娠は禁忌とされる，3つの心疾患，①PH，②DCM，③マルファン症候群について，妊産婦死亡につながるリスク因子について，母体予後良好群および不良群に分けて後方視的に検討した。

なお，妊娠中の心機能評価として，NYHA (New York Heart Association)分類，心エコー，ホルター心電図，血中脳性ナトリウム利尿ペプチド(Brain Natriuretic Peptide，BNP)濃度を用いた。

① 肺高血圧症(PH)

PH25症例を，予後良好群(Termまでもったもの)9症例，予後不良群(Pretermで分娩となったもの)16症例に分けて，母体死亡に繋がるリスク因子を解析した。

患者背景を表3に示す。分娩週数，帝切率，児の出生体重において，両群間に有意差を認めた。しかし，妊産婦死亡は25例中の1例で，全体の4%にあたり，文献的に報告される30～50%よりは低い数値であった。PHの内訳は，PPHは3例，Eisenmenger症候群4例，先天性心疾患術後9例，先天性心疾患非術後4例，慢性肺塞栓1例，急性肺塞栓1例，僧帽弁狭窄症1例，膠原病1例，C型肝炎1例であった。

まず，NYHA分類の妊娠中の変化と分娩週数について検討した(図2)。その結果，妊娠前または初期にNYHA Ⅱ度以上のものは，Ⅰ度に比べて，妊娠後期に有意に増悪(カイ二乗検定，$p<0.01$)し，1例を除く全例が帝王切開となり，母体適応による早産となった。また，1例は母体死亡となった。

次に，妊娠中の肺動脈圧の変化について検討した(図3)。なお，肺高血圧の定義は，心臓カテーテル検査では安静時の平均肺動脈圧が25mmHg 以上，あるいは，心臓超音波検査での肺動脈の推定収縮期圧が 30mmHg 以上とした[4]。まず，心臓カテーテルの推移を図3の左に示す。心カテ施行群は重症なものも多く，多くが，母体適応による早産となった。心エコー(図3右)では，妊娠初期の推定収縮期肺動脈圧が，50 mmHg未満のものは，Termまで妊娠継続可能であった。妊娠初期の肺動脈圧が，50 mmHg以上のものは，いずれも母体適応により人工早産となった。

② 拡張型心筋症(DCM)

DCMは，その発症時の定義を，左室短縮率(FS：Fractional shortening)<30%あるいは，左室拡張末期径(LVDd:Left ventricular end diastolic dimension)>48mmとした。19例21妊娠を母体の予後良好群15妊娠，予後不良群6妊娠に分け検討した。予後不良群は，妊産婦死亡あるいは心不全発症例とした。患者背景を表4に示す。予後不良群では，分娩週数が早く，妊産婦死亡も6例中3例と有意に多く認めた。

まず，妊娠週数に伴うNYHA分類の変化について検討した(図4)。予後不良群においては，

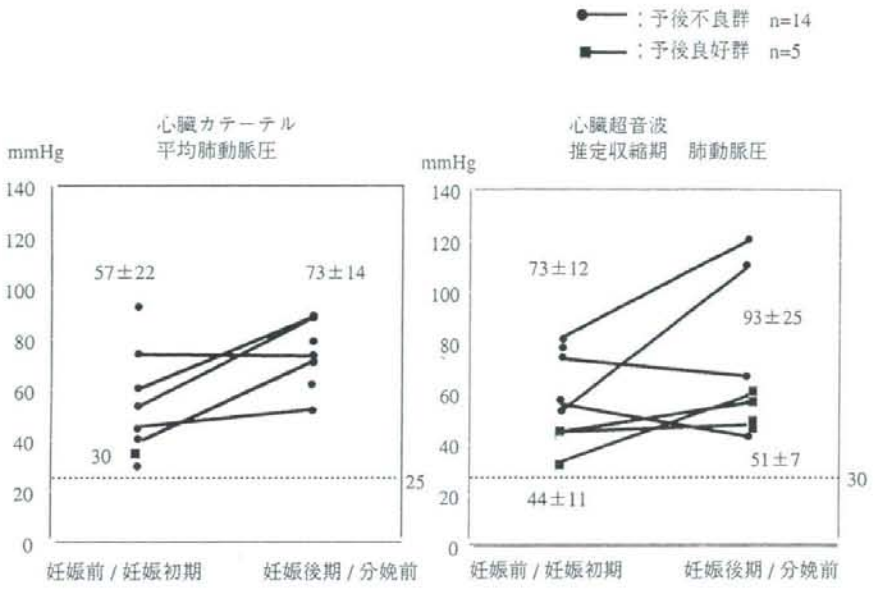

図3．肺高血圧症における妊娠中の肺動脈圧の変化

表4．拡張型心筋症における母体予後良好群および予後不良群の患者背景

	予後良好群 (n=15)	予後不良群 (n=6)
分娩時平均年齢(歳)	29.2	29.9
平均経妊回数	0.3	1.7
平均経産回数	0.3	1.3
帝王切開	7/15	4/6
早産**	3/15	6/6
分娩週数(週)**	37.2	32.3
出生時体重(g)*	2.634	2,023
妊産婦死亡*	0/15	3/6
胎児・新生児死亡	0/15	2/6

*p<0.05, **p<0.01

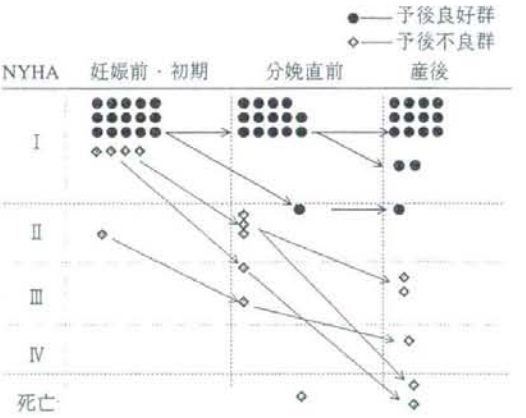

図4．拡張型心筋症における妊娠中のNYHAの変化(n=21)

妊娠前あるいは初期のNYHAⅠ度であるものが，その後，NYHAⅡ度以上に多くが悪化し，妊娠前あるいは初期のNYHA分類は母体の予後予測因子とはなり得なかった。

次に，心エコーによる，妊娠中のFSの変化について検討した(図5)。予後良好群は，22%以上で推移し，妊娠経過中増悪傾向は認めなかった。しかし，予後不良群は，FSは22%未満であり，妊産婦死亡例(術中，産褥1～6ヵ月で死亡)例は10%未満であった。さらに，予後不良群は全例，妊娠と関連した発症であった。

妊娠中のLVDdの変化を検討した(図6)。予後良好群，予後不良群，さらに妊産婦死亡例において，明らかな差は認めなかった。

つまりLVDdは，母体の予後予測因子とはなり得ない。したがって，DCMの妊娠時の管理においては，FS，発症時期が妊娠関連か否か

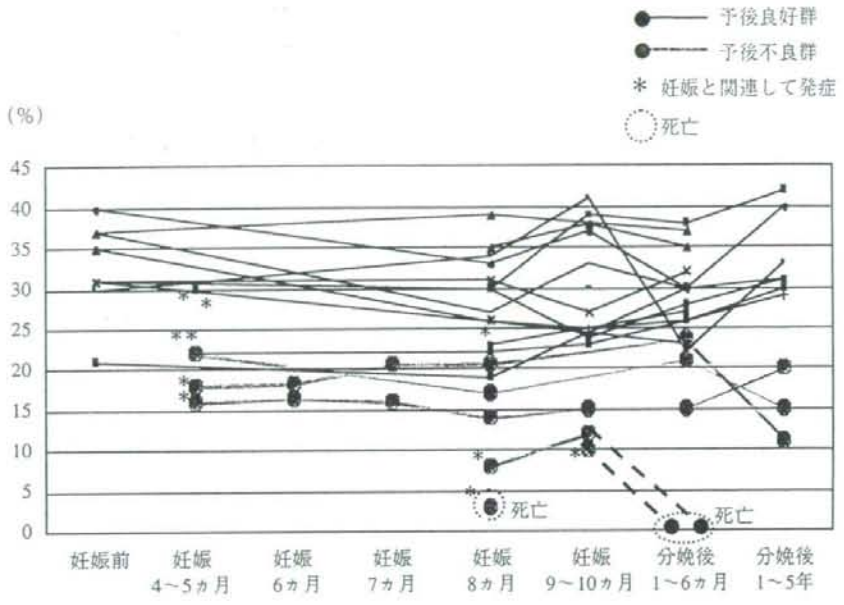

図5. 拡張型心筋症における妊娠中の左室短縮率の変化

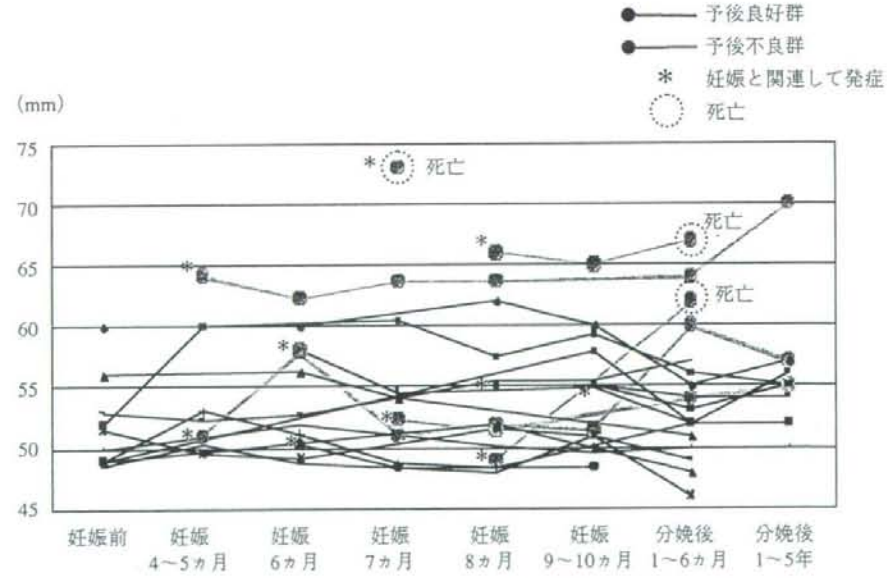

図6. 拡張型心筋症における妊娠中の左室拡張末期径の変化

が，母体の予後予測因子となるよい指標であると考えられた。

③マルファン症候群

22例28妊娠を母体予後良好群(非解離例17妊娠)および不良群(解離例11妊娠)に分けて検討した。患者背景を表5に示す。帝切率のみ解離例に有意差を認めた。また，妊産婦死亡，新生児死亡は認めず。なお，解離例のうち当院で妊娠初期から管理した症例は7妊娠，解離発症後の母体搬送・紹介例は4妊娠あり，妊娠中

表5. マルファン症候群合併妊娠の患者背景

	解離症例 (n=11)	非解離症例 (n=17)
分娩時平均年齢(歳)	29.5	30.1
平均経妊回数	0.6	0.7
平均経産回数	0.4	0.3
C/S*	7/11	2/17
早産	4/11	5/17
分娩週数(週)	36.5	37.5
出生時体重(g)	2,702	2,754
妊産婦死亡	0/11	0/17
新生児死亡	0/11	0/17

*p<0.05

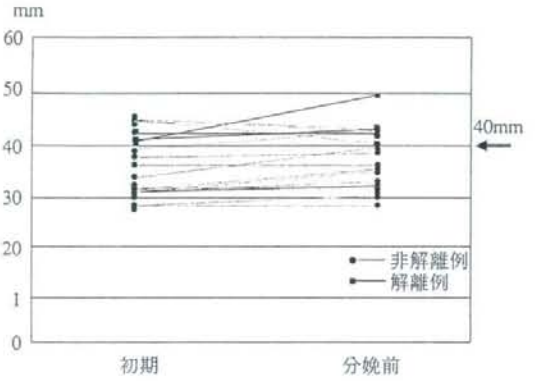

図7. 妊娠中のバルサルバ洞血管径の変化

の解離発症でマルファン症候群と気づかれる症例も多く認めた。

まず，マルファン症候群合併妊娠における，各診断基準項目の適合率を比較検討したが，両群間に有意差は認めなかった。次に，突然死あるいは大動脈解離発症を有する家族歴と妊娠中あるいは産褥の大動脈解離発症の関連について検討した。まず，家族歴を有する者は，非解離症例で9/12(75%)，解離症例で7/10(70%)であったが，突然死あるいは解離発症の家族歴を有する者は，非解離症例で4/12(33%)であるのに対し，解離症例で6/10(60%)であり，解離症例で多い傾向にあった。さらに，妊娠中のバルサルバ洞血管径の変化での検討では(図7)，妊娠初期の径が40mm以上のものは，40mm未満に比べ有意に解離のリスクが高く(カイ二乗検定，P<0.05)また，妊娠中に急激な拡大を認めるものも注意を要した。

表6. 産褥心機能の非悪化群および悪化群における，患者背景および育児背景(n=57)

	心機能非悪化群 (n-49)	心機能悪化群 (n=8)
分娩時平均年齢(歳)	30.2	31.6
分娩週数(週)	37.2	35.8
帝王切開施行例(%)	46.9	100
授乳あり	35(80%)	8(100%)
授乳回数(回/日)	7.5回(5～12)	7.1回(5.5～8)
睡眠時間	6.5時間(4～9)	5.8時間(4～8)
家族の支援	5/17	2/4

以上，3疾患のハイリスク心疾患合併妊娠の検討により，母体の予後推定因子として，以下の因子が考えられた。PHにおいては，妊娠前・初期のNYHA分類および肺動脈圧，DCMにおいては，FS，発症時期が妊娠と関連するか否か，マルファン症候群においては，突然死あるいは大動脈解離の家族歴の有無，妊娠初期のバルサルバ洞径が挙げられた。

3)心疾患合併妊娠の，産褥心機能評価についての検討

先の表1にも示したように，妊産婦死亡の時期は，2ヵ月から5ヵ月といった，産褥期に多く認められる。この時期の，授乳に代表される育児負担に着目し，産褥心機能との関係について検討した。対象は，妊娠中から，分娩後3ヵ月以上フォローアップした，57例とした。心機能悪化の指標として，心エコーによる左心機能低下，心電図所見の悪化，自覚症状の悪化のいずれか1つ以上とした。心機能非悪化群49例，悪化群8例，これらの患者背景を表6の上段に示す。両群間の分娩時平均年齢，分娩週数，帝王切開率に有意差は認めなかった。産褥心機能と育児負担について検討したものを表6の下段に示す。授乳については，非悪化群では，35/49例(80%)であるのに対し，