

Table 6. Characteristics of Drugs for the Treatment of Pulmonary Hypertension During Pregnancy and Lactation

Drug	Class	Pregnancy categories	Characteristics/ adverse effects	Teratogenicity	Breast feeding	Package insert* ¹	
						Pregnancy	Lactation
Beraprost	Prostacyclin	B	Oral	Absent	Probably compatible	1	1
Epoprostenol	Prostacyclin	B	Drip infusion	Absent	Probably compatible	2	1
Bosentan	Endothelin receptor antagonist	X	Oral, Hepatic disorder	Unknown* ²	Potential toxicity	1	2
Sildenafil	PDE III inhibitor		Oral, Visual disorder			2	1

PDE III, phosphodiesterase III.

(Note) The above information is based on "Drugs in pregnancy and lactation, 8th edition (2008)"⁴⁰ (Blank columns represent no information in the source material).

*¹Information on the use during pregnancy and lactation in the package insert.

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.

*²Bosentan has been reported teratogenic in animals, but the risk for teratogenicity is unclear in humans.

[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 7. Classification of Valvular Heart Diseases by Maternal and Fetal Risks

Low maternal/fetal risk factors		High maternal/fetal risk factors
Aortic stenosis	Asymptomatic; Normal left ventricular function; Mean pressure gradient <25 mmHg; Orifice area >1.5 cm ²	Severe stenosis; Complicated with severe pulmonary hypertension; Left ventricular dysfunction
Aortic regurgitation	NYHA Class I to II; Normal left ventricular function	NYHA Class III to IV; Complicated with severe pulmonary hypertension; Left ventricular dysfunction
Mitral stenosis	No severe pulmonary hypertension; Orifice area >1.5 cm ² ; Mean pressure gradient <5 mmHg	NYHA Class II to IV; Complicated with severe pulmonary hypertension; Left ventricular dysfunction
Mitral regurgitation	NYHA Class I to II; Normal left ventricular function	NYHA Class III to IV; Complicated with severe pulmonary hypertension; Left ventricular dysfunction
Mitral valve prolapse	No mitral regurgitation, or Mild to moderate mitral regurgitation but normal left ventricular function	
Pulmonary stenosis	Mild to moderate stenosis	
<ul style="list-style-type: none"> • High maternal/fetal risk factors <ul style="list-style-type: none"> - Complicated with severe pulmonary hypertension (pulmonary artery pressure is ≥75% of systemic blood pressure) - Left ventricular dysfunction (LVEF<40%) - Using mechanical valves requiring anticoagulation therapy - Marfan syndrome • Low maternal/fetal risk factors <ul style="list-style-type: none"> - Normal left ventricular function (LVEF>50%) 		

LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

2. Pulmonary Hypertension (Table 6)

In women with pulmonary hypertension, pregnancy will increase pulmonary artery pressure, worsen right heart failure, and worsen ventilation-perfusion ratio mismatch. The risk during pregnancy and childbirth in patients with pulmonary hypertension is extremely high. It is strongly recommended that women with pulmonary hypertension avoid pregnancy by using reliable contraception, and prompt artificial termination of pregnancy, if occurs, should be considered whenever necessary.⁷⁰⁻⁷² If a patient decided to continue pregnancy after understanding the risk, she must be hospitalized at an appropriate timing to monitor the progress and perform childbirth under careful management by a special team.⁷³⁻⁷⁵ Since death immediately after childbirth may often occur, the mother must be monitored for about 1 week in the intensive care unit. The outcome does not differ by delivery method (cesarean section vs. vaginal delivery) and anesthesia (general anesthesia vs. local anesthesia).⁷⁶

3. Valvular Heart Diseases

Table 7 describes the guidelines for pregnancy and childbirth in patients with valvular heart diseases⁴⁶ and Table 8 lists anticoagulation and antiplatelet therapies during pregnancy.

Figure shows a flow chart of anticoagulation therapy during pregnancy in patients using mechanical valves that is commonly practiced in Japan empirically rather than based on scientific data.⁷⁷ During the first trimester of pregnancy, patients should receive unfractionated heparin or low molecular weight heparin^{78,79} rather than warfarin^{80,81} which may cause malformation in the fetus. At 14 weeks of gestation or thereafter, either subcutaneous heparin or oral warfarin should be selected. Since heparin is not highly reliable in terms of the prevention of thrombosis, oral warfarin therapy is a preferable method for the mother. At 36 weeks of gestation, oral warfarin should be replaced by continuous intravenous administration of heparin. Cesarean section is preferable since staff members and instrument can be scheduled in advance.

Drug	Class	Pregnancy categories	Characteristics/ adverse effects	Teratogenicity	Breast feeding	Package insert*	
						Pregnancy	Lactation
Warfarin	Coumarin derivative	D	- Teratogenic (osteogenesis/ chondrogenesis, cerebral nervous system) - Bleeding complication in the fetus	Present	Compatible	1	1
Heparin	Unfractionated heparin	C	- Promote decalcification during long-term treatment (bone fracture in the mother) - Higher incidence of thrombosis than warfarin	Absent	Compatible	1	
Enoxaparin		B	- Heparin-induced thrombocytopenia has been reported	Absent	Compatible	2	2
Dalteparin	Low molecular weight heparin	B	- Not indicated for the prevention of thrombosis in patients with cardiovascular disease	Absent	Compatible	1	1
Aspirin (low-dose)	Antiplatelet effect	C	- Considered relatively safe - Contraindicated in 28 weeks of gestation or thereafter regardless of the dose	Absent	Potential toxicity	2	1
Dipyridamole	Antiplatelet effect	B	Hypotension, worsening of anginal symptoms	Absent	Probably compatible	2	1
Ticlopidine	Antiplatelet effect	B	Bleeding, liver disorder	Absent	Potential toxicity	2	1

Note) The above information is based on "Drugs in pregnancy and lactation, 8th edition (2008)".⁴⁰

*Information 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 confirmed. 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. It is desirable that the drug be given after lactation is stopped.

[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.

4. Aortic Diseases

See Table 9 for recommendations for patients with Marfan syndrome.^{82,83}

See Table 10 for recommendations for patients with Takayasu disease.^{84,85}

Patients with unrepaired congenital coarctation of the aorta may experience severe complications such as hypertension, left heart failure, aortic aneurysm formation and aortic dissection during pregnancy. When the patient shows aortic dilatation and develop hypertension during pregnancy, management with bed rest and β -blockers are required. Periodic blood pressure monitoring is necessary since a decrease in blood pressure reduces blood flow in the placenta. It is preferable that the patient undergo surgery or catheter intervention to repair coarctation of the aorta before pregnancy. The risk during pregnancy to the mother and fetus is low in patients following repair of coarctation of the aorta. However, patients with hypertension or aortic dilatation should be managed with β -blockers.

5. Cardiomyopathy

Women with hypertrophic cardiomyopathy, even those with chest pain, exertional dyspnea and/or syncope before pregnancy, will rarely experience worsening of signs/symptoms during pregnancy, and may tolerate pregnancy in most cases. The risk is believed high in those with a maximum wall thickness of ≥ 30 mm, those with a history of cardiac arrest or sustained ventricular tachycardia, those with recurrent syncope, and those with a family history of sudden death: The risk of pregnancy/childbirth should be carefully evaluated for these patients.^{86,87}

Fatal heart failure is rare in women with dilated cardiomyopathy when heart failure is compensated and remained in NYHA Class I, and drug therapy may be discontinued during pregnancy. However, severe heart failure may develop in some cases during the third trimester, and careful consideration is required even for patients with mild heart failure.^{88,89}

Peripartum cardiomyopathy develops most commonly in the first month after childbirth. Cardiac function returns to normal by 6 months after childbirth in about 50% of patients, but the prognosis of patients with persistent and progressive

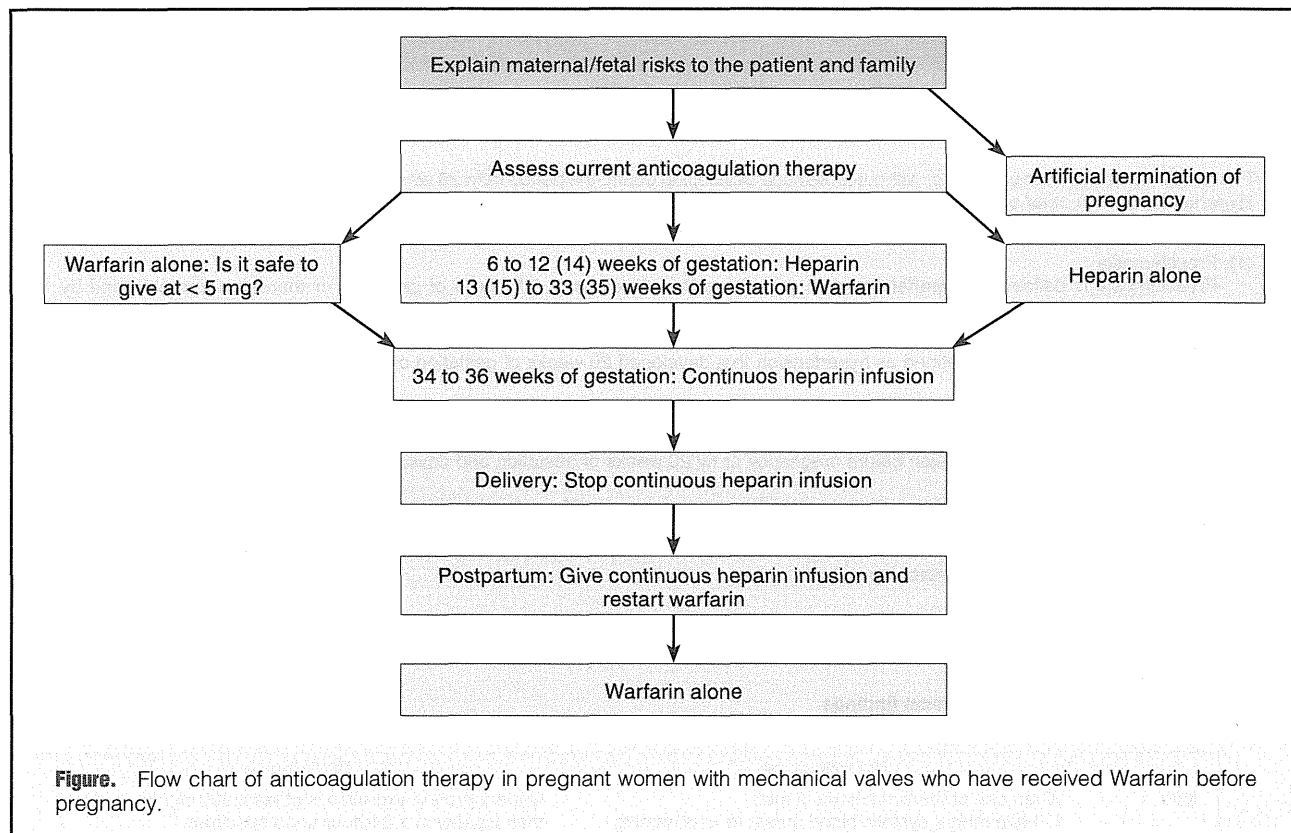


Table 9. Important Points of Management for Patients With Marfan Syndrome During Pregnancy and Childbirth

1. Explain that there is a 50% possibility of inheriting the disease.
2. Encourage the patient to undergo surgery before pregnancy, if indicated.
3. Instruct the patient to avoid pregnancy when the ascending aortic diameter (including Valsalva sinus) is 44 mm or larger or when aortic dissection is present. Patients with aortic diameter of 43 mm or smaller should be explained that they can become pregnant but may develop aortic dissection.
4. Patients with an ascending aortic diameter of <40 mm may have normal vaginal delivery.
5. Mitral regurgitation should be treated according to the guidelines for the treatment of valvular heart diseases.
6. β -blockers should be given whenever necessary with careful consideration of the potential effects on the mother and fetus.
7. Perform strict blood pressure control and pain management.

Table 10. Important Points of Management for Patients With Takayasu Disease During Pregnancy and Childbirth

1. It is reported that patients with untreated atypical coarctation of abdominal aorta may develop renal hypertension, which may lead to heart failure and renal failure. The prognosis of these patients is poor since sepsis and pregnancy-induced hypertensive nephropathy may develop.
2. Atypical coarctation of the aorta should be treated according to the recommendations for the treatment of coarctation of the aorta.
3. Aortic regurgitation should be treated according to the recommendations for the treatment of valvular heart diseases.
4. Aortic aneurysms (including annuloaortic ectasia) should be treated according to the recommendation for Marfan syndrome.
5. Ischemic heart disease (coronary ostial narrowing): Consider for surgery before pregnancy.
6. Hypertension should be treated with β -blockers. ACE inhibitors and angiotensin receptor blockers should be avoided.
7. Steroid therapy should be continued, but treatment at higher doses is rarely required.
8. Patients should be observed for autoimmune disorders and connective tissue diseases (collagen diseases).

ACE, angiotensin converting enzyme.

Table 11. Definition and Classification of Pregnancy Induced Hypertension: Proposed by Japan Society of Obstetrics and Gynecology, 2005**1. Term**

Pregnancy toxemia should be referred to as pregnancy induced hypertension (PIH).

2. Definition

PIH is defined as hypertension with or without proteinuria developing during the period from 20 weeks of gestation to 12 weeks of postpartum. Hypertension due to other complications is not PIH.

3-1. Classification of PIH**(1) Preeclampsia**

Preeclampsia is defined as hypertension with proteinuria that develops at 20 weeks of gestation or thereafter and subsided by 12 weeks of postpartum.

(2) Gestational hypertension

Gestational hypertension is defined as hypertension that developed 20 weeks of gestation or thereafter and subsided by 12 weeks of postpartum.

(3) Superimposed preeclampsia

Patients with superimposed preeclampsia include:

- 1) Women who have hypertension before pregnancy or by 20 weeks of gestation and develop proteinuria at 20 weeks of gestation or thereafter.
- 2) Women who have hypertension and proteinuria before pregnancy or by 20 weeks of gestation and experience worsening of hypertension and/or proteinuria at 20 weeks of gestation or thereafter.
- 3) Women who have proteinuria as the only sign of renal disease before pregnancy or by 20 weeks of gestation and develop hypertension at 20 weeks of gestation or thereafter.

(4) Eclampsia

Eclampsia is defined as the first onset of convulsions not related to epilepsy or secondary convulsions at 20 weeks of gestation or thereafter. Eclampsia is classified into antepartum eclampsia, intrapartum eclampsia and puerperal eclampsia according to the timing of onset.

3-2. Subclassification based on clinical findings**(1) Disease type by clinical findings**

	Hypertension	Proteinuria
Mild	When one of the two criteria is met: 1. 140mmHg ≤ systolic blood pressure <160mmHg 2. 90mmHg ≤ diastolic blood pressure <110mmHg	Urinary protein excretion is at least 300mg/day and less than 2g/day in a 24-hour urine specimen
Severe	When one of the two criteria is met: 1. Systolic blood pressure is ≥160mmHg 2. Diastolic blood pressure is ≥110mmHg	Urinary protein excretion is ≥2g/day, or spot urinary protein level is ≥300mg/dl in more than 3 consecutive samples from fresh urine

(2) Disease type by timing of onset

Those developing by 32 weeks of gestation are referred to as early onset type, and those developing at 32 weeks of gestation or thereafter as late onset type.

[Remarks]

- (1) Gestational proteinuria (proteinuria that is first detected at 20 weeks of gestation or thereafter and subsides by 12 weeks of postpartum) is not included in PIH typing.
- (2) Chronic hypertension may often lead to superimposed preeclampsia, and should be managed carefully as in the case of PIH. Worsening of chronic hypertension is not included in PIH typing.
- (3) Pulmonary edema, cerebral hemorrhage, premature separation of the normally implanted placenta, and HELLP syndrome* are not always caused by PIH, but are critical illness closely related to PIH. These findings are not included in PIH typing.
- (4) The type of PIH is expressed using h and H for mild and severe hypertension, p and P for mild and severe proteinuria, EO for early onset type, LO for late onset type, S for superimposed type, and C for eclampsia. For example, the type of preeclampsia may be expressed with Hp-EO and hP-LO, gestational hypertension with H-EO and h-LO, superimposed preeclampsia with Hp-EOS and hP-LOS, and eclampsia with HP-EOSC and hP-LOSC.

*HELLP syndrome is characterized by Hemolysis, Elevated Liver enzyme and Low Platelets, and develops during pregnancy (often at 27 weeks of gestation or thereafter) and the puerperal period.

Cited from *Acta Obstetrica et Gynaecologica Japonica* 2006; 58: N61–N70.¹⁰³

left ventricular dysfunction is poor.^{88,89} In patients who continue to show a left ventricular ejection fraction (LVEF) of ≤ 50% after childbirth, cardiac function may often decrease to cause death during or after the next pregnancy. Contraception is strongly recommended for such patients.⁹⁰ Most effects on the fetus develop in the third trimester or after birth, and the incidences of low birth weight infants and stillbirth are slightly higher than in healthy women.

6. Arrhythmias

Patients with congenital heart disease associated with arrhyth-

mias are often treated and monitored carefully for arrhythmia during pregnancy. In patients following repair of congenital heart disease, arrhythmia may newly develop or worsen during pregnancy and childbirth.^{91,92} Since atrial flutter/fibrillation, atrial tachycardia, ventricular tachycardia, severe atrio-ventricular block, and other conditions may cause significant hemodynamic changes that highly affect the mother and fetus, appropriate diagnosis and emergency treatment are commonly required.^{73,93} Pregnant women with risk factors for development of arrhythmia (eg, those with heart failure, those with pre-existing arrhythmia before pregnancy, and those with a history of tachyarrhythmia) should undergo regular checkups more frequently during pregnancy.

Table 12. Characteristics of Antihypertensive Drugs Commonly Used During Pregnancy and Lactation

Drug	Class	Pregnancy categories*1	Characteristics/ adverse effects	Teratogenicity*1	Breast feeding	Package insert*2	
						Pregnancy	Lactation
Methyldopa	Central antihypertensive	B	Lassitude, thirst Used in Europe and the United States	Absent	Probably compatible	2	1
Clonidine	Central antihypertensive	C	Few reports	Absent	Probably compatible	2	
Atenolol	β -blocker	D	IUGR, hypoglycemia, bradycardia	Absent	Potential toxicity	2	1
Propranolol	β -blocker	C→D	IUGR, hypoglycemia, bradycardia	Absent	Potential toxicity	2	1
Metoprolol	β -blocker	C→D	IUGR, hypoglycemia, bradycardia	Absent	Potential toxicity	1	1
Oxprenolol	β -blocker	C→D	IUGR, hypoglycemia, bradycardia	Absent	Potential toxicity	1	1
Labetalol	β -blocker	C	IUGR, hypoglycemia, bradycardia	Absent	Probably compatible	1	1
Sotalol	β -blocker	B→D	Bradycardia	Absent	Potential toxicity	2	1
Hydralazine	Peripheral vasodilator	C	Headache, neonatal thrombocytopenia	Absent	Probably compatible	2	1
Nifedipine	Calcium channel blocker	C	Headache, palpitation, hypotension	Absent	Probably compatible	1	1
Nicardipine	Calcium channel blocker	C	Headache, palpitation, hypotension	Absent	Probably compatible	1	1
Isosorbide dinitrate	Nitrate	C	Few reports	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	Angiotensin receptor blocker*4	C→D	Fetal renal dysplasia, renal failure, oligohydramnios	Present*4	Probably compatible	1	1
Losartan*4	Angiotensin receptor blocker*4	C→D	Fetal renal dysplasia, renal failure, oligohydramnios	Present*4	Probably compatible	1	1
Furosemide	Diuretic	C (D)	Disturbance of utero-placental circulation, fetal dehydration	Absent	Probably compatible	2	1
Spirolactone	Diuretic	C (D)	Possible feminization	Absent	Probably compatible	2	1
Hydrochlorothiazide	Diuretic	C (D)	Thrombocytopenia, hemolytic anemia	Absent	Compatible	2	1

ACE, angiotensin converting enzyme; IUGR, intrauterine growth retardation.

Note) The above information is based on "Drugs in pregnancy and lactation, 8th edition (2008)".⁴⁰

*1B→D/C→D: Pregnancy category B or 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. The safety in pregnant women has not been established.

*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.

7. Ischemic Heart Disease

Although the incidence of acute myocardial infarction (AMI) during the perinatal period is quite rare (1 in 10,000 cases), the incidence is expected to increase in the future.^{94,95} Smoking and hypertension are the most significant risk factors for development of AMI during the perinatal period.⁹⁶ AMI is

more common in women who have had children, and the most common lesion is the anterior wall. β -blockers are the first-line therapy to prevent myocardial infarction (MI). Low-dose aspirin is effective in preventing myocardial ischemic attacks during pregnancy. Many reports have described that thrombolytic therapy for the treatment of AMI is not teratogenic to the fetus and the prognosis of the mother and fetus is favorable.⁹⁷ Percutaneous coronary intervention and coronary artery bypass

grafting during pregnancy are also effective.^{98,99}

Patients with coronary aneurysms in Kawasaki disease do not have significant problems during pregnancy and childbirth when coronary stenosis is absent and cardiac function is normal. Patients who have coronary stenosis, those after MI and those after coronary intervention may experience a progression of ischemic disease or a worsening of heart failure during pregnancy and childbirth.^{100,101}

8. Heart Failure

Volume overload and tachycardia during pregnancy may worsen heart failure. The severer the heart failure during pregnancy, the higher the mortality of the mother and the incidences of premature birth, intrauterine growth retardation and abortion or stillbirth. Women with NYHA Class III or severer

heart failure should be recommended to avoid pregnancy and terminate pregnancy promptly when they become pregnant.^{94,102} There are no established data indicating the safety of pregnancy in patients in certain levels of ejection fraction.

9. Hypertension (Tables 11,¹⁰³ 12)

Patients with hypertension may prone to have premature birth, intrauterine growth retardation, perinatal death, and other perinatal disorders related to pregnancy-induced hypertension. The incidences of premature separation of the normally implanted placenta and perinatal death are high in patients with pregnancy-induced hypertension.^{104,105} They are often prone to have such as malignant hypertension, cerebral hemorrhage, heart failure, and renal dysfunction.

IV Important Points in Obstetric Management

Table 13. Expected Annual Pregnancy Rates With Different Contraceptive Methods

Methods	General use	Optimal use
No contraception	85%	85%
Coitus interruptus (extravaginal ejaculation)	27%	4%
Tracking menstrual cycle, sexual abstinence	25%	1 to 9%
Condom	15%	2%
Pessary	16%	6%
Oral contraceptives	8%	0.3%
Intrauterine contraceptive device	0.1 to 0.8%	0.1 to 0.6%
Tubal ligation	0.5%	0.5%
Vasoligation	0.15%	0.1%

Cited with modification from "Guidelines for the use of low-dose contraceptive pills: second edition" in 2006¹⁰⁶ proposed by Japan Society of Obstetrics and Gynecology.

Table 14. Incidence of Neurological Sequelae in Liveborn Infants by Gestational Age at Birth

	Hospitalized	Dead (%)	Disability
≤24 weeks	20	12 (60)	1 (13)
24 to 27 weeks	158	19 (12)	30 (22)
28 to 31 weeks	311	18 (6)	37 (13)
≥32 weeks	3,478	87 (3)	30 (1)

Data in 1984 to 1997 from the Maternal and Perinatal Center, Tokyo Women's Medical University Hospital.

Table 15. Methods of Administration of and Contraindications to Tocolytics

Methods of administration	
Ritodrine (β -stimulant)	Start at 50 μ g/min, and increase the dose by 50 μ g/min in every 10 to 20 minutes.
Terbutaline (not indicated in Japan)	Start at 10 μ g/min, and increase the dose by 5 μ g/min in every 10 minutes.
Magnesium sulfate	Administer 4 g intravenously over 30 minutes, and continue infusion at 2 to 4 g/hr by monitoring blood magnesium concentration in the mother until uterine contraction subsides.
Indomethacin (not indicated in Japan)	Administer 25 to 50 mg intrarectally or orally every 6 hours for ≤48 hours.
Contraindications	
Ritodrine (β -stimulant)	Poorly controlled diabetes, pulmonary hypertension
Magnesium sulfate	Hypocalcemia, myasthenia gravis, renal failure
Indomethacin (not indicated in Japan)	Peptic ulcer, blood disorders, hepatic/renal insufficiency, asthma, pancreatitis, proctitis, obstetric bleeding

1. Contraception (Table 13)¹⁰⁶

2. Effects of Hemodynamic Condition of the Mother on the Fetus

When progressive worsening of maternal health to a life-threatening condition is expected, physicians should consider for termination of pregnancy (artificial abortion or early delivery). When the growth in the fetal head circumference stops due to progressive worsening of maternal condition, pregnancy should be terminated (for early delivery).

3. Timing of Delivery

The timing of delivery should be determined by considering the survival and incidence of neurological sequelae by weeks of gestation at delivery. The prognoses of infants born with a body weight of <1,000 g and infants born earlier than 28 weeks of gestation are poor¹⁰⁷ (Table 14).

4. Controlling Uterine Contraction

Patients with impending abortion or premature labor are indicated for tocolytics (Tables 15, 16),¹⁰⁸ while patients who need

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 flushing, 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	
<ul style="list-style-type: none"> • 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	
<ul style="list-style-type: none"> • 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	
<ul style="list-style-type: none"> • 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

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 anomaly	○		●			●		◎	
Complete transposition of the great arteries						●		○	
Mustard operation	●					●		○	
Coarctation of the aorta	●		●			●	●	●	
Pulmonary valve atresia + ventricular septal 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)".⁴⁰

*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	
Spirolactone	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)"⁴⁰ (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, contractions, 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 effi-

ciently. 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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Appendix

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Members:

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- Yoshihito Hata, Division of Cardiovascular Medicine, Adult Congenital Heart Disease Center, Jichi Medical University
- Tomoaki Ikeda, Department of Obstetrics and Gynecology, Mie University Graduate School of Medicine
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- Norifumi Nakanishi, Department of Cardiovascular Internal Medicine, National Cerebral and Cardiovascular Center

- Satoshi Nakatani, Division of Functional Diagnostics, Department of Health Sciences, Osaka University Graduate School of Medicine
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(The affiliations of the members are as of September 2011)



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

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Kaoru Kawasaki, MD; Takakazu Miyoshi, MD; Yoshihito Sasaki, MD, PhD;
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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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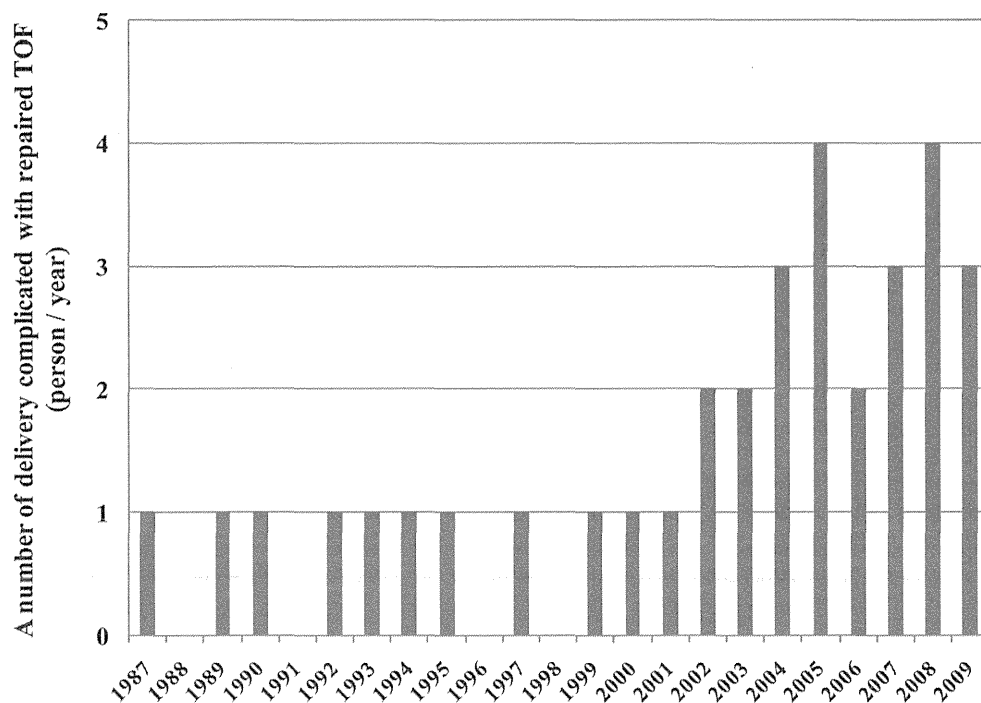


Figure 1. Annual number of deliveries complicated with repaired TOF at the National Cerebral and Cardiovascular Center. TOF, tetralogy of Fallot.

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) $\geq 1,500$ ml).⁶ Offspring events were defined as small-for-gestational-age (SGA, birth weight $< 10^{\text{th}}$ 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 \pm 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.

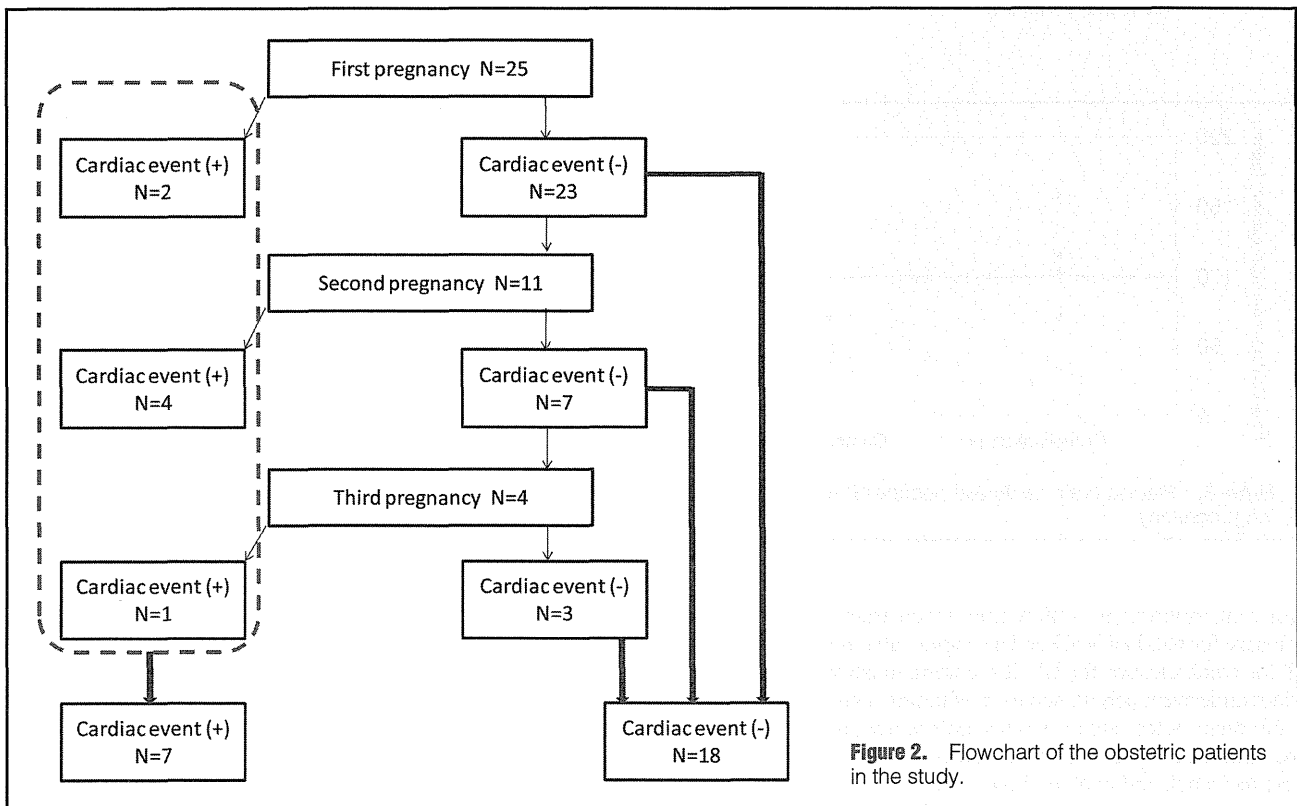


Figure 2. Flowchart of the obstetric patients in the study.

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 ini-

tially 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

	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.

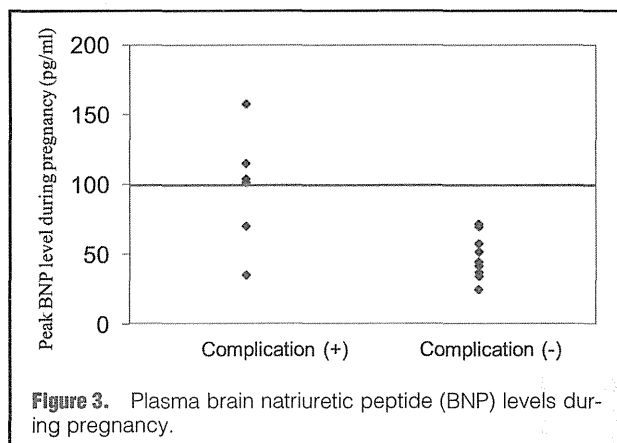


Figure 3. Plasma brain natriuretic peptide (BNP) levels during pregnancy.

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 inhibitors before or immediately after pregnancy. Three patients had a smoking habit.

Pregnancy Course

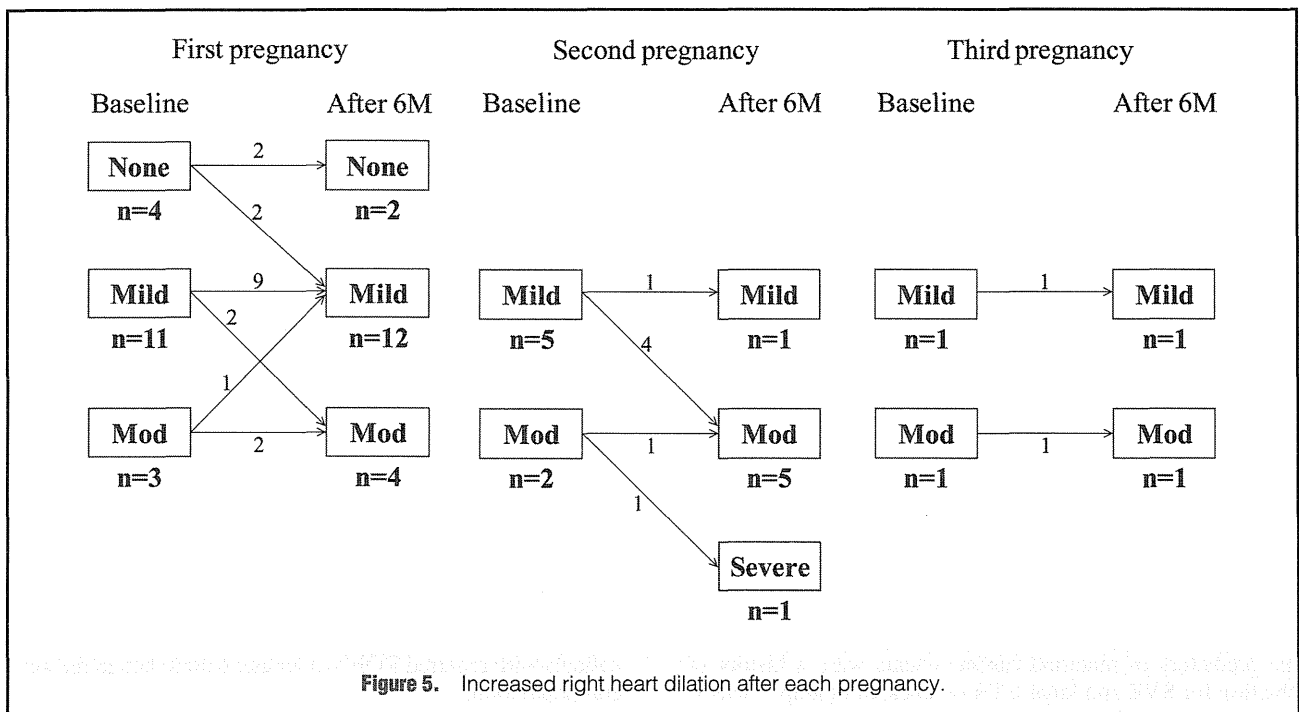
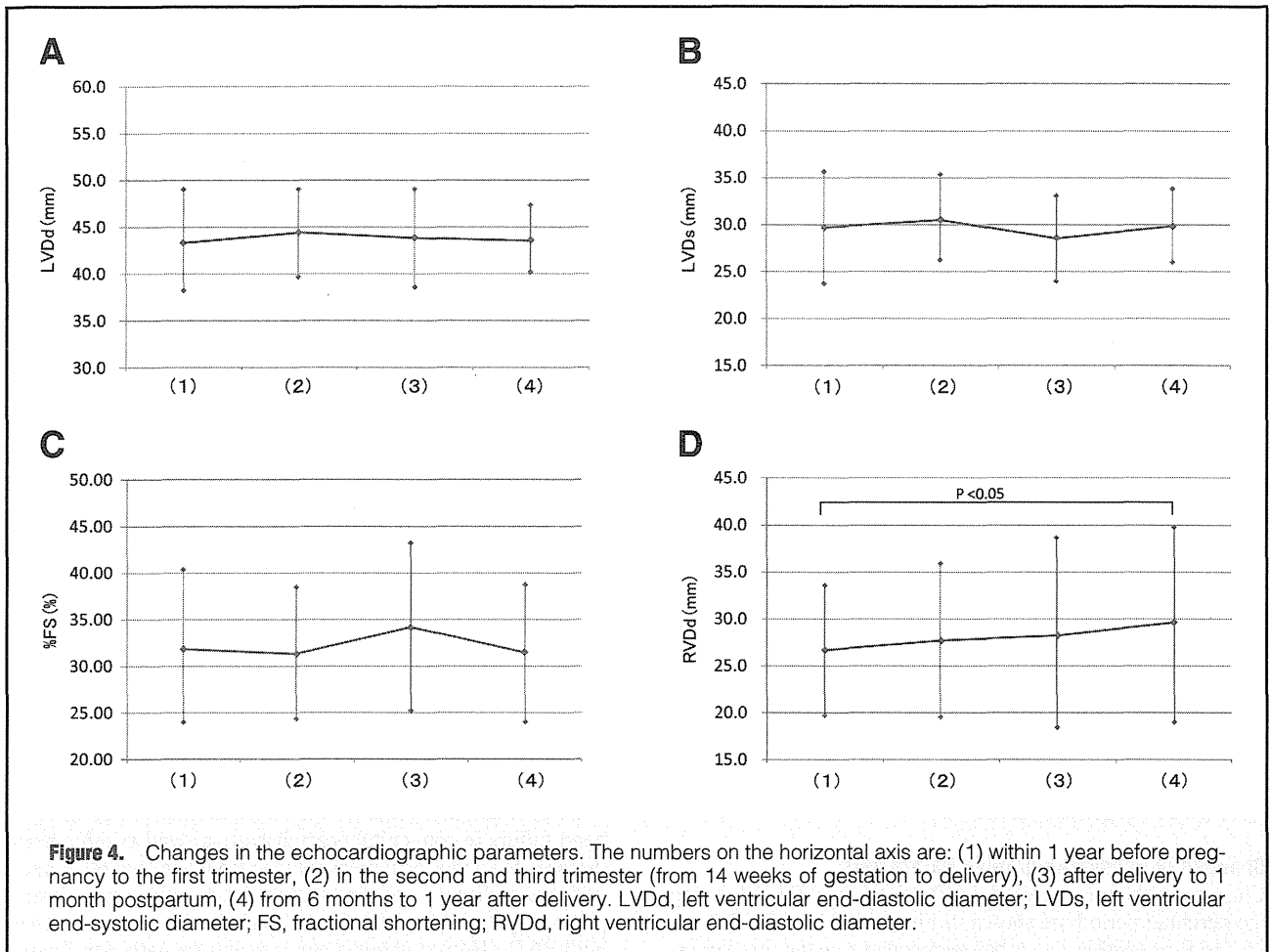
The mean age at delivery was 29.1 years (range: 20–39 years); 14 patients had 1 delivery, 7 had 2 deliveries, and 4 had 3 deliveries. All pregnancies were singletons. All patients delivered successfully at a mean of 37.8 weeks of gestation (range: 30–41 weeks). There were 29 vaginal deliveries and 11 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



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 \pm 6.9 mm within 1 year before pregnancy to the first trimester, 27.7 \pm 8.9 mm in the second and third trimester, 28.2 \pm 10.1 mm after delivery to 1 month postpartum, and 29.6 \pm 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 replacement¹⁰ 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 \geq 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 \leq 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 \leq 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