

## Review Article



# Adult Congenital Heart Disease with Pregnancy

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### Conflict of Interest

The author has no financial conflicts of interest.

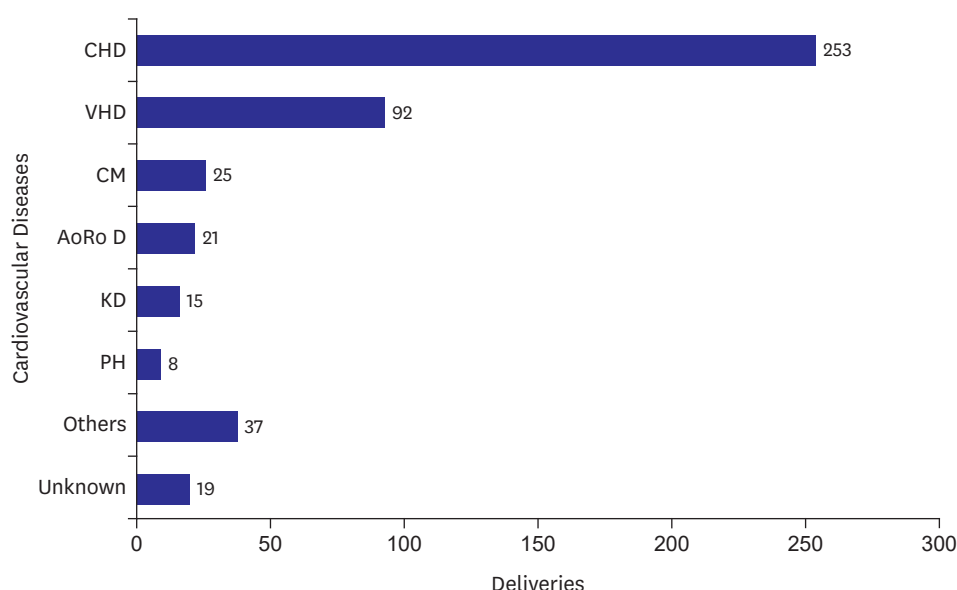
## ABSTRACT

The number of women with congenital heart disease (CHD) at risk of pregnancy is growing because over 90% of them are grown-up into adulthood. The outcome of pregnancy and delivery is favorable in most of them provided that functional class and systemic ventricular function are good. Women with CHD such as pulmonary hypertension (Eisenmenger syndrome), severe left ventricular outflow stenosis, cyanotic CHD, aortopathy, Fontan procedure and systemic right ventricle (complete transposition of the great arteries [TGA] after atrial switch, congenitally corrected TGA) carry a high-risk. Most frequent complications during pregnancy and delivery are heart failure, arrhythmias, bleeding or thrombosis, and rarely maternal death. Complications of fetus are prematurity, low birth weight, abortion, and stillbirth. Risk stratification of pregnancy and delivery relates to functional status of the patient and is lesion specific. Medication during pregnancy and post-delivery (breast feeding) is a big concern. Especially prescribing medication with teratogenicity should be avoidable. Adequate care during pregnancy, delivery, and the postpartum period requires a multidisciplinary team approach with cardiologists, obstetricians, anesthesiologists, neonatologists, nurses and other related disciplines. Caring for a baby is an important issue due to temporarily pregnancy-induced cardiac dysfunction, and therefore familial support is mandatory especially during peripartum and after delivery. Timely pre-pregnancy counseling should be offered to all women with CHD to prevent avoidable pregnancy-related risks. Successful pregnancy is feasible for most women with CHD at relatively low risk when appropriate counseling and optimal care are provided.

**Keywords:** Pregnancy; Delivery; Congenital heart disease

## INTRODUCTION

Advances in medical and surgical treatments have led to more than 90% of children with congenital heart disease (CHD) surviving into adulthood. Most surgical interventions, however, are not curative, and many adults with CHD face the prospect of late complications such as cardiac failure, arrhythmia, thrombosis, pulmonary hypertension (PH), aortopathy, and unexpected sudden cardiac death etc., and followed by further reoperation. The burden of pregnancy and delivery represents a new challenge in women with CHD (**Figure 1**). Those with PH, severe left ventricular (LV) outflow tract stenosis, cyanotic CHD, aortic root dilatation/



**Figure 1.** Incidence of structural heart disease in pregnancy in Japan. In 138 departments of obstetrics in Japan, 80,455 pregnancies were underwent during 2002 to 2003, 769 of them (0.96%) were from women with cardiovascular disease. Four hundred and seventy (0.58%) were structural heart disease and CHD is the most frequent with 245 of 470 (52.1%).

AoRo D = aortic root disease; CHD = congenital heart disease; CM = cardiomyopathy; KD = Kawasaki disease; PH = pulmonary hypertension; VHD = valvular heart disease.

aneurysm, cardiac dysfunction, Fontan procedure, Kawasaki disease (KD) with coronary artery stenosis, mechanical valve carry a high risk for both the mother and the fetus (**Table 1**).<sup>1)2)</sup>

While many women with CHD tolerate the hemodynamic changes of pregnancy, others may face significant immediate or late risks of pregnancy including volume overload, arrhythmias, progressive cardiac dysfunction, thrombosis and death (**Figure 2**) during pregnancy, delivery and the postpartum especially in women with moderate to severe CHD, but fortunately, most of these complications could be managed. Management of complications is firstly rest, followed by medication and intervention (catheter or surgery), in some cases, termination is necessary if fetus is enough growing, especially after 28 or 30 weeks of gestation. Those are expected to develop heart failure during pregnancy and delivery should be repaired before becoming pregnant if feasible. For women with CHD and significant arrhythmias, and when those are expected to develop arrhythmias and hemodynamic compromise during pregnancy, ablation could be done before pregnancy. Management and prophylaxis of infective endocarditis is also mandatory. Leg care is important prevention for thromboembolism especially in patients with

**Table 1.** Women with CHDs requiring careful monitoring during pregnancy or strongly recommended to avoid pregnancy

Types
• PH (Eisenmenger syndrome)
• LV outflow or inflow tract stenosis (severe AS with a mean pressure gradient of >50 mmHg)
• Heart failure (NYHA class III to IV, LV ejection fraction <35%)
• Marfan syndrome (ascending aortic diameter at end-diastole >40 mm)
• Mechanical valves
• Cyanotic CHD (arterial oxygen saturation <85%)
• Fontan procedure
• KD with coronary artery aneurysm and stenosis
• Arrhythmias those induce hemodynamic compromise

AS = aortic stenosis; CHD = congenital heart disease; KD = Kawasaki disease; LV = left ventricular; NYHA = New York Heart Association; PH = pulmonary hypertension.

<ul style="list-style-type: none"> <li>• <b>Maternal risk</b> <ul style="list-style-type: none"> <li>– Maternal death</li> <li>– Other potential complications to consider (<i>than death</i>): <ul style="list-style-type: none"> <li>» Stroke/Arrhythmia</li> <li>» Overt Heart Failure</li> <li>» Adverse effect on cardiovascular function and thus, prognosis</li> </ul> </li> </ul> </li> <li>• <b>Fetal risk</b> <ul style="list-style-type: none"> <li>– Recurrence of CHD</li> <li>– Preterm delivery/IUGR/embryopathy/intracranial bleeding/lactation</li> </ul> </li> </ul>
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**Figure 2.** Risk of pregnancy in women with CHD.  
CHD = congenital heart disease; IUGR = intrauterine growth restriction.

moderate to severe CHD. Complications of fetus include growth failure, abortion and stillbirth, and retinal and lung complication due to immaturity (**Figure 2**), and transmission of CHD from mother to fetus is another important issue.

## CARDIOVASCULAR AND OTHER PHYSIOLOGICAL CHANGES DURING PREGNANCY AND DELIVERY

### Hemodynamic changes

Hemodynamics during pregnancy and delivery is significantly affected by changes in fluid circulation, hematology, respiratory function, endocrinology and autonomic nervous system (**Tables 2 and 3**) (**Figure 3**).<sup>2,3)</sup> Plasma volume begins to increase from 4 weeks of gestation, peaks at 32 weeks of gestation, and then is maintained at a similar level or increase gradually to the volume 40–50% higher than before pregnancy.<sup>4,5)</sup> Heart rate peaks at around 32 weeks of gestation to about 20% higher than before pregnancy. Tidal volume increases by 18–25%, and cardiac output increases to 30–50% higher than before pregnancy at 20–24 weeks of gestation, and is maintained at a similar level throughout the pregnancy.<sup>5)</sup> Aortic pressure and systemic vascular resistance decrease during pregnancy. In late pregnancy, low blood pressure can happen due to compression of inferior vena cava by enlarged uterus, especially in right decubitus position or during lying on the back. Pulmonary artery pressure remains similar throughout pregnancy because of increased pulmonary blood volume with decreased

**Table 2.** Hemodynamic changes during pregnancy, labor and delivery

Hemodynamic changes
<ul style="list-style-type: none"> <li>• During pregnancy <ul style="list-style-type: none"> <li>– Cardiac output increase by 60–80%</li> <li>– Blood volume increase by 40–50% increase</li> </ul> </li> <li>• During labor and delivery <ul style="list-style-type: none"> <li>– Increase in blood volume with uterine contraction (300–500 mL)</li> <li>– Increase in venous return</li> <li>– Blood loss during delivery by 400–500 mL in vaginal delivery and 800–900 mL in Caesarean section</li> </ul> </li> </ul>

**Table 3.** Physiological changes during pregnancy, other than hemodynamics

Physiological changes
<ul style="list-style-type: none"> <li>• Hematological: hypercoagulable state, anemia</li> <li>• Respiratory change: Increased tidal volume</li> <li>• Aortic wall: fragmentation of medial elastic fiber</li> <li>• Autonomic nervous system: increase heart rate by 20%</li> <li>• Hormonal: increase cortisol, estrogen, and RAAS</li> </ul>

RAAS = renin-angiotensin-aldosterone system.

1. Major changes in hemodynamics, hormones, catecholamine, autonomic nervous system and psychological condition during pregnancy and delivery
2. Specific co-existing hemodynamics of CHD, surgical scars
3. Genetic abnormalities
4. Underlying cardiac failure, arrhythmogenicity

**All these contribute to the outcome of pregnancy in women with heart disease**

**Figure 3.** Hematologic changes during pregnancy.  
CHD = congenital heart disease.

pulmonary vascular resistance. Cardiac function during pregnancy is affected by these changes of preload and afterload. In the first trimester, arterial pulse is characterized by a rapid rise. Jugular venous pulse becomes more conspicuous especially after 20 weeks of gestation. The first heart sound becomes louder with widely splitting second heart sound. Pulmonary systolic murmur is common because of augmented volume load with increased heart rate.

During delivery, hemodynamics is influenced by posture of the body, mode of delivery, labor, and type of anesthesia. Uterine contraction and labor pain causes increases in circulatory volume by 300–500 mL, cardiac output by 15–25% and heart rate and blood pressure.<sup>3)</sup> It is preferable that women in labor is kept in the left decubitus, because uterus compresses the inferior vena cava and abdominal aorta during lying on the back. Typical blood loss during vaginal delivery is about 400–500 mL, while that during cesarean section is about 800–900 mL. This blood loss, labor and pain could induce rapid hemodynamic change, therefore, painless delivery method with vaginal delivery is a preferred method for women with moderate to severe CHD or women with New York Heart Association (NYHA) functional class >II. Immediately after delivery, venous return increases abruptly after the pressure on the inferior vena cava from the enlarged uterus is relieved. These drastic hemodynamic changes could have a negative impact on cardiac function, and it could induce cardiac dysfunction or cardiac failure. Heart rate, blood pressure and cardiac output return rapidly to normal. In women with CHD, recovery of hemodynamics and cardiac function after delivery takes longer (4–6 months after delivery) time than in those with normal heart.<sup>3)</sup> In high-risk pregnancy, women with originally decreased cardiac function, this cardiac dysfunction continues much longer than those with normal heart or mild CHD, or sometimes it could not recover to pre-pregnant status even long after delivery.

### **Hematological changes: hypercoagulable state and anemia**

Red blood cell counts increase by 20–30% along with increased production of erythropoietin, but relative anemia happens due to increased plasma volume during pregnancy. White blood cell counts increase up to 13,000/mm especially neutrophils.<sup>2)</sup> Platelet counts slightly decreases. In late pregnancy, anticoagulant factors such as plasma fibrinogen, von Willebrand factor and coagulation factors I, V, VII, VIII, X, and XII are activated. Also, fibrinolytic inhibitors (plasminogen activator inhibitor [PAI]-1 and PAI-2) are activated. The risk of thromboembolism increases during late pregnancy. Therefore, because of this hypercoagulability, meticulous care must be taken for women with mechanical valve, KD with coronary artery aneurysm or atrial fibrillation (AF) and those prone to have deep vein thrombosis, typically Fontan patients. During the first and second trimesters, hemoglobin and hematocrit levels decrease, which causes a relative anemia. In severe cases, ferrous supplementation therapy is necessary.

### Respiratory change

Respiratory physiology is altered early in pregnancy because of chemically induced hyperventilation due to increased progesterone levels. There are an increased minute ventilation (45% increase) and intake volume, but vital capacity is stable, and residual volume decrease by 40%.<sup>2)</sup> Later in pregnancy lung volume reserve decreases due to elevation of diaphragm, then, breathlessness is common even in normal pregnancy.

### Great arterial wall

Fragility of arterial wall increases during pregnancy due to increased production of estrogen that has been held responsible for interference with collagen turnover, which in conjunction with elastic fiber results in fragmentation of elastic lamella. Relaxin in the serum during pregnancy causes a decrease in collagen synthesis. So-called cystic medial necrosis (especially fragmentation of medial elastic fiber) in the aorta is observed during normal pregnancy and that increases aortic diameter and stiffness. This is adaptive response for increased blood volume to placenta. Since aortic wall becomes fragile during pregnancy, aortic dissection may occur in susceptible patients such as Marfan syndrome associated with dilated aorta.<sup>6)7)</sup>

### Autonomic nervous system

Heart rate increases by 20% and heart rate variability (HRV) is significantly suppressed during pregnancy.<sup>8)</sup> Impaired autonomic nerve activity, volume overload of the heart and operative scar all play a role on tachyarrhythmia during pregnancy in CHD patients. Reduced HRV may be a predictor of tachyarrhythmia during pregnancy.<sup>8)</sup> Close monitoring for tachyarrhythmia in patients with previous reparative surgery for CHD during pregnancy is, thus, warranted.

### Hormonal changes

There is an increase in cortisol, estrogen and renin-angiotensin-aldosterone system (RAAS) during pregnancy. However, relation between hormonal changes and hemodynamic changes are remains unclear.

## CARDIAC ASSESSMENT BEFORE PREGNANCY

It is important for women with CHD to undergo appropriate assessment of pulmonary artery pressure, ventricular function, aortic diameter, cyanosis, NYHA functional classification, and cardiopulmonary exercise test (CPX) to predict the risk of pregnancy-related complications in the mother and fetus. Pre-pregnancy checkup for patients with CHD includes history taking, physical examination, chest X-ray, electrocardiogram (ECG), and echocardiography. CPX or exercise ECG test is also important to evaluate tolerability and risk of pregnancy and delivery in women with CHD.<sup>9)</sup> Cardiac catheterization and Holter monitoring may be also conducted whenever necessary.

Factors affecting pregnancy and delivery in women with CHD are as follows:

- a. Major changes in hemodynamics, hormones, catecholamines, the autonomic nervous system, and psychological condition during pregnancy and delivery
- b. Specific co-existing hemodynamics of CHD
- c. Genetic abnormalities
- d. Underlying cardiac failure, arrhythmogenicity, PH, aortopathy

All these factors contribute to the outcome of pregnancy in women with CHD.

Assessment of pregnancy risk should include detailed cardiac, surgical and obstetric history, physical examination, documentation of oxygen saturations, 12-lead ECG and transthoracic echocardiography.<sup>11)</sup> Maternal functional status is an important determinant of outcome and should be documented. Exercise stress testing provides an objective measure of functional capacity and can assess blood pressure response to exercise in women with aortic stenosis (AS). Chronotropic incompetence during stress testing predicts pregnancy complications.<sup>9)10)</sup> Stress echocardiography is helpful to assess ischemia in women with coronary anomalies/disease and to assess ventricular reserve in women with cardiomyopathies or valve lesions. Magnetic resonance imaging (MRI) is useful to define complex CHD anatomy, assess right ventricular (RV) size and function and visualize the aorta/aortic arch.

There are a number of risk assessment tools to predict maternal cardiac complications during pregnancy including: World Health Organization (WHO) classification,<sup>12)</sup> Cardiac Disease in Pregnancy (CARPREG) risk score,<sup>13)</sup> and Pregnancy and Congenital Heart Disease (ZAHARA) risk score.<sup>14)</sup> The CARPREG risk score assigns one point to each of 4 predictors of adverse maternal cardiac events. The risk of a cardiac event in pregnancy increases from 5% for a woman with a score of 0 to 27% with a score of 1 and 75% when the score is  $\geq 2$ .<sup>13)</sup> The ZAHARA risk score incorporates 8 weighted clinical predictors to quantitate pregnancy risk on a scale of 0–13.<sup>14)</sup> The risk of cardiac complications increases from 2.9% with a score of 0–0.50 to 70% with a score  $>3.51$ . In addition to these general risk scores, it is also important to consider lesion-specific risks as described below (PREGNANCY AND DELIVERY IN WOMEN WITH VARIOUS CHDS INCLUDING HIGH-RISK PREGNANCY).

## PRE-PREGNANCY COUNSELING, ASSESSMENT OF PREGNANCY RISKS

Preconception counseling is an important aspect of cardiac care for women with CHD and should begin early, ideally in adolescence, by cardiologists and maternal–fetal medicine specialists with experience in pregnancy and CHD. Despite surgical repair, many women with CHD will have residua, sequelae and late complications those could have important implications for pregnancy. Women who have not regular cardiac care prior to pregnancy should be re-assessed by a cardiologist in early pregnancy.

Counseling should include general recommendations for a healthy pregnancy such as weight control, cessation of smoking and periconceptional folic acid supplementation. Specific cardiac recommendations include education on the maternal and fetal risks, contraception advice, pre-pregnancy optimization of blood pressure, modification of fetotoxic medications, interventions to optimize pregnancy outcomes and, when appropriate, the potential late effect of pregnancy on the heart as well as maternal life expectancy.<sup>1)15-18)</sup> Counseling should also include a detailed obstetric history, including an assessment of the risk of complications such as pregnancy-induced hypertension and diabetes mellitus that might impact on cardiovascular function. Pregnancy-induced hypertension may cause an increase in afterload and potential deterioration in cardiac function.<sup>19)20)</sup> There may be persistent cardiovascular abnormalities following pregnancy.<sup>21)</sup> These changes can be detrimental, specifically in the setting of structural heart disease/CHD.

### Maternal risk

Women with CHD should receive pre-pregnancy counseling, including discussion about the risk to the mother and fetus, hereditary risk, possible course of pregnancy, and sexual activity and caring for baby. It is likely that women with CHD experience heart failure and/or arrhythmia during pregnancy and after delivery, and encounter difficulties in caring for baby due to poor cardiac function. Although the NYHA classification is often used to consider whether pregnancy is recommended or not, physicians must not rely solely on it to predict the prognosis of pregnancy of their individual patients. **Table 1** lists patients with CHD and conditions that require careful monitoring during pregnancy or should be advised to avoid pregnancy. These CHD are high-risk for both the mother and fetus. These can develop cardiac failure, arrhythmias, thromboembolism, cardiac ischemia, aortic dissection, or increase cyanosis.

### Fetal risk

Maternal health is an important determinant of fetal and neonatal health. Fetal mortality (1.7%) and perinatal mortality (2.3%) are still rare, but increased above the baseline rate of 1%.<sup>22)</sup> Fetal and perinatal morbidity is more common, ranging between 16% and 18% and primarily includes low-birth-weight babies (8%), prematurity (16%), and the complications of prematurity.<sup>13)22)</sup> The incidence of fetal and neonatal complications varies depending on the cardiac lesion. Risk of transmission of CHD to offspring is dependent on the maternal or paternal cardiac condition. For CHD not associated with a genetic syndrome, transmission to offspring is in the range of 3–5% with higher rates in left-sided outflow tract lesions such as AS (10%).<sup>23)</sup> There is also a risk of congenital anomalies in women with diabetes. Most antenatal cardiac screening is done at 20–22 weeks of gestation and better performed by someone trained fetal cardiac imaging.

## PREGNANCY AND DELIVERY IN WOMEN WITH VARIOUS CHDS INCLUDING HIGH-RISK PREGNANCY

In women with Eisenmenger syndrome, severe LV out flow tract stenosis (mean pressure gradient >50 mmHg), cardiac failure (>NYHA III with LV ejection fraction <35%), aortic root dilatation (Marfan with aortic root size >45 mm, bicuspid aortic valve (BAV) with aortic root size >50 mm, it should better avoid or terminate pregnancy, or become pregnant after surgical repair (**Table 1**).

Pregnancy and delivery in women with various CHDs are mentioned below.

### Eisenmenger syndrome

Pulmonary artery hypertension presents a serious risk during pregnancy, particularly when the pulmonary pressure exceeds 70% of systemic pressure, irrespective of functional class.<sup>24)</sup> Eisenmenger syndrome refers to cardiac defects associated with high pulmonary vascular resistance, reversal or bi-directional shunting flow at the great vessel, ventricular or atrial level and cyanosis. Pregnancy in women with Eisenmenger syndrome is associated with a high maternal mortality; reported ranges have been between 28% and 50%.<sup>25)26)</sup> Death was observed especially after delivery (sudden death, cardiac failure, thromboembolism, and pulmonary artery dissection). Weiss et al.<sup>25)</sup> conducted a retrospective analysis of 73 pregnancies in women with Eisenmenger syndrome between 1978 and 1996, and found maternal mortality was 36%, and timing of death was during pregnancy in 3 and at delivery



or within 1 month postpartum in 23. Causes of death were sudden death, heart failure, thromboembolism, and pulmonary artery dissection. Mode or timing of delivery and anesthesia had no relation with maternal mortality. In the University of California, Los Angeles (UCLA) experience,<sup>26)</sup> 9 of 16 pregnant women with Eisenmenger syndrome had spontaneous or artificial abortion, and the other 7 completed delivery. No one died, but 6 experienced deterioration, severe hemorrhage and/or syncope especially after delivery, and 5 of them delivered low birth weight infant.

Small contemporary series have suggested that outcomes may be more optimistic.<sup>27)</sup> There is growing experience using pulmonary vasodilators during pregnancy.<sup>27-29)</sup> Curry et al.<sup>29)</sup> reported 12 pregnancies in 9 women, and 2 maternal deaths (both were before year 2000), 9 live births (mean birth weight of 2,197 g at 34 weeks and 3 miscarriages were observed. They recommended sildenafil, prostanoids, anticoagulation administration and Caesarean section with general anesthesia, and uterine compression sutures. The risks of sildenafil in pregnancy may be low, but there has been no satisfied experience on this medication. So even there were these successes, Eisenmenger syndrome is still associated with significant risk to the fetus and neonate including recurrent miscarriage, intrauterine growth retardation, prematurity and death. Because of the high-risk nature of this condition, pregnancy is generally discouraged. For women who elect to continue pregnancy, it is important that they have care by an experienced multidisciplinary team that includes a PH specialist.

### Complete transposition of the great arteries (TGA)

Almost all women with TGA have undergone some forms of surgical repair including atrial switch operation (Mustard/Senning), arterial switch operation (ASO; Jatene) or extraconduit repair (Rastelli). The type of surgical correction is a major determinant of the associated residua, sequelae and late complications, which are risks of pregnancy. Overall, women with TGA have residua and/or sequelae that can confer risk for adverse cardiac events in pregnancy.

#### Women with TGA and atrial switch operation

Women with Mustard/Senning operations often have systemic RV dysfunction and/or tricuspid valve regurgitation and brady/tachyarrhythmias. Pregnancy may result in worsening of systemic RV function or tricuspid valve regurgitation.<sup>30)</sup>

According to Drenthen et al.,<sup>31)</sup> in 69 pregnancies in 28 women with TGA and atrial switch operation, maternal complications were common (25%) including arrhythmias (22%) and thromboembolism (4%), and also fetal complications were high (premature delivery in 31%, small for gestational age in 22% and spontaneous/elective abortions in 29%).

In other reports,<sup>30)32)</sup> RV failure with progressive tricuspid regurgitation was observed in 10–25%, and it continued in some women even after delivery. Long-term prognosis of this RV dysfunction is still unknown. A high incidence of fetal complications was also observed, but risk factors for pregnancy and delivery are not yet clarified.

#### Women with TGA and ASO

Pregnancies in women with ASO are increasingly common as this cohort of women with TGA reach childbearing age. Pregnancy outcomes in these women have not been well studied. There is a one paper on this topic.<sup>33)</sup> Seventy-four women of childbearing age were identified, and 9 of them had 17 pregnancies. Six women (67%) had clinically important valve (n=5) and ventricular (n=1) lesions before pregnancy. There were 4 miscarriages. Cardiac complications



developed in 2 women during pregnancy; an impaired LV systolic function followed by a non-sustained ventricular tachycardia in 1, and a mechanical systemic atrioventricular valve thrombosis in 1. There was no maternal death.

### **Congenitally corrected transposition of the great arteries (CCTGA)**

CCTGA is defined by discordant atrioventricular and ventriculo-arterial connections. CCTGA can occur in isolation or in conjunction with other cardiac lesions such as ventricular septal defect (VSD) and/or pulmonary stenosis. Other than double switch operation or Rastelli type procedure, women with CCTGA continue to have a morphologic systemic right ventricle after repair. This is associated with various degrees of ventricular dysfunction and systemic tricuspid valve regurgitation. Tricuspid valve regurgitation is severer than those observed in complete TGA after atrial switch. Connolly et al.<sup>34)</sup> reported 60 pregnancies in 22 women with CCTGA resulted in 50 live births (83%) with a mean birth weight of 3.2 kg. There were 44 (88%) vaginal deliveries. There was no maternal death, but heart failure was observed in 2.

Successful pregnancy can be achieved in most women with CCTGA, but risk factors for pregnancy are systemic RV dysfunction, tricuspid valve regurgitation. Also, complete atrioventricular block is not rare, and those could deteriorate cardiac function during pregnancy.<sup>35)</sup> Pregnancy and delivery are well tolerated if RV function is preserved before pregnancy.

### **Fontan circulation**

Fontan operation refers to a procedure for single ventricular physiology, where systemic venous blood is diverted into the lung, bypassing the subpulmonary ventricle. Preconception risk stratification is very important because some will be at very high-risk for pregnancy complications of the cardiac (heart failure, refractory arrhythmias, and thrombosis) and non-cardiac (liver disease, edema, and protein losing enteropathy) complications. The most common problems encountered during pregnancy are arrhythmias (25%) and systolic and diastolic heart failure (5%).<sup>36)37)</sup> Fetal complications are common and include premature birth (32%), intrauterine growth retardation (12%), and fetal death (4%).<sup>22)</sup>

Pregnancy in these patients is generally high-risk and preconception counseling and contraception practices vary widely. High rates of miscarriage, prematurity, and small for gestational age babies are reported. Termination and delivery could be often considered after 28–30 weeks of gestation when maternal or fetal condition deteriorated rapidly. It is not yet known whether long-term prognosis in these patients is affected by pregnancy. In very high-risk patients such as so-called not good Fontan, pregnancy is not recommended.

Around 20 years ago, Canobbio et al.<sup>36)</sup> reported 33 pregnancies in women with Fontan, and 2 developed tachyarrhythmias (1 atrial flutter, 1 paroxysmal supraventricular tachycardia) during pregnancy. However, no cardiovascular complications during labor, delivery or early postpartum were observed. There were 15 (45%) live births, 13 spontaneous abortions and 5 elective terminations. Authors concluded that pregnancy in women with Fontan may be tolerable, but there is high-risk for miscarriage. The tendency to routinely discourage pregnancy may need to be reconsidered. Ten years later after report of Canobbio's study,<sup>36)</sup> Drenthen et al.<sup>37)</sup> reported 10 pregnancies from 6 of 38 women with Fontan procedure (age of 18–45 years). There were 5 miscarriages (50%) and 1 aborted ectopic pregnancy. Remaining 4 live-birth pregnancies, clinically significant complications were encountered, NYHA class deterioration, AF, pregnancy-induced hypertension, premature delivery, fetal growth retardation and neonatal death. Four of the other 7 attempted to become pregnant, but they

reported infertile. Moreover, several important menstrual cycle disorders were documented. Incidence of primary amenorrhea was high (15/38, 40%). They concluded that women with Fontan could successfully complete pregnancy when Fontan palliation is adequate without important late complications, although it is often complicated by clinically significant non-cardiac events. In addition, subfertility or infertility and menstrual disorders were common.

### Cyanotic CHD

Women with cyanotic CHD face greater challenge and higher risks than those with complex CHD with normal oxygen saturation. There is a right to left shunting at the level of atria, ventricles or great vessels. During pregnancy, maternal blood becomes more hypercoagulable especially after 28 weeks of gestation, therefore, the risk of red blood cell slugging and thrombosis formation increases. This may manifest as a deep vein thrombosis, pulmonary thrombosis, or stroke. Deep vein thrombosis could be a source of paradoxical emboli. The role of preventive anticoagulation is controversial. The cyanosis also has inherent coagulation abnormalities. This may be exaggerated by use of anti-coagulants.<sup>38)</sup> The fall in afterload during pregnancy may augment the right to left shunting and accelerate cyanosis that possibly induces deterioration. The fetal risks relate to the severity of maternal cyanosis. With increasing maternal cyanosis, fetal growth delay becomes more prominent and infants are likely to have low birth weight and prematurity. Spontaneous abortion is more likely in the first trimester. Presbitero et al.<sup>39)</sup> reported 96 pregnancies in 44 women with cyanotic CHD (excluding Eisenmenger syndrome), there were 1 maternal death (infective endocarditis) and 32% maternal cardiovascular complications such as heart failure in 8, thromboembolism in 2, supraventricular tachycardia in 2, and infective endocarditis in 2. There were 41 live births (43%), and 15 of them were premature and only 26 were term delivery. There were high incidences of miscarriage (57%) and low birth weight infant (mean birth weight of 2,575 g). In women with oxygen saturation level of 85% or lower, the rate of live birth was as low as 12%. Connolly and Warnes<sup>38)</sup> collected data on 25 pregnancies in 15 women with cyanotic complex pulmonic atresia (non-operated in 4, post-palliative surgery in 3, and post-repaired in 8), and found 10 live births (1 twin), 6 abortions, and 9 miscarriages (45%). There were no maternal deaths and 1 heart failure during pregnancy.

### Tetralogy of Fallot (TOF)

Almost all pregnant women with TOF will have undergone an intracardiac repair in childhood. Although pulmonary regurgitation and RV volume overload are common after TOF repair, this group of women does well during pregnancy.<sup>40)41)</sup> Pregnancy outcomes relate to the severity of pulmonary regurgitation, the size and systolic function of ventricles and supraventricular or ventricular arrhythmias. Women with unrepaired or only palliated TOF have chronic cyanosis, which has much higher rates of maternal cardiovascular complications.<sup>39)</sup> The right heart tends to be enlarged in the late postpartum period, and pregnancy may also affect the long-term prognosis of patients with repaired TOF.<sup>42)</sup>

Akagi et al.<sup>43)</sup> collected data from 143 pregnancies in 98 women (median age 27 year) with repaired TOF. NYHA functional classifications were class I in 133 (93%) and class II in 10 (7%). Estimated RV pressure was 41 mmHg (range: 19–90) and moderate to severe pulmonary regurgitation was complicated in 41 (29%). There were no maternal deaths, full-term birth in 117 (82%), premature birth in 14 (10%, 8 of 14 with scheduled preterm), miscarriage in 8 (5%), and abortion in 4 (3%). There was vaginal delivery in 68% and Caesarian section in 31% (cardiac indication in 11%). Worsening of arrhythmia was found in 6% during pregnancy, and 2% during or after delivery. Heart failure was observed in 6%

during the pregnancy and 5% after the delivery. Those with NYHA class II had significant higher risk for developing heart failure.

### Ebstein disease

Ebstein disease is associated with tricuspid regurgitation, an abnormal functional RV and a dilated right atrium. Patients may also have multiple accessory pathways. Women of childbearing age with Ebstein disease may or may not have undergone a tricuspid valve repair. Women with unrepaired Ebstein disease will have variable degrees of tricuspid regurgitation and abnormalities of the functional RV. These factors are important determinants of pregnancy outcome. Pregnancy is well tolerated when there is reasonable RV size and systolic function, the absence of significant arrhythmias or cyanosis. The most common complications are supraventricular tachycardia/AF and heart failure.<sup>44)</sup> Patients with Ebstein disease with NYHA I can tolerate well with pregnancy and delivery, but fetal wastage rate is high. Pre-pregnant ablation of supraventricular tachycardia is recommended in patients with Ebstein disease and supraventricular tachycardia due to Wolff-Parkinson-White (WPW) syndrome before becoming pregnant.<sup>45)</sup>

Connolly and Warnes<sup>44)</sup> reported details of 111 pregnancies in 44 women with Ebstein anomaly, resulting in 85 live births (76%). Seventy-six deliveries (89%) were vaginal, and 9 (11%) were by Caesarean section. There were 23 premature deliveries, 19 spontaneously abortions, 7 therapeutic abortions, and 2 early neonatal deaths. The mean birth weight of infants born to cyanotic women was 2.53 kg, in contrast, that to acyanotic women was 3.14 kg. Transmission rate was 6%. There were no serious pregnancy-related maternal complications. Niwa<sup>45)</sup> reported 57 pregnancies in 26 females with age of 31±4.4 years: NYHA I in 56, NYHA II in 2, tricuspid valve replacement (mechanical valve) in 1, tricuspid valve plasty in 3 and catheter ablations in 5. There were no maternal deaths, and maternal complications were heart failure in 1, supraventricular tachycardia in 4 and thrombotic valve in 1. There was Caesarean section in 10, and vaginal delivery in 27. There were 37 deliveries/20 abortions (abortion rate: 35%) with a mean birth weight of 2,610±650 g (1,200–3,600 g).

### Congenital AS and BAV

Most congenital AS is secondary to BAV. In general, mild or moderate AS is well tolerated for pregnancy. Women with severe AS who are symptomatic should have an intervention prior to pregnancy. Asymptomatic women with severe AS generally may become symptomatic during pregnancy and require careful preconception risk stratification. Complications such as heart failure and arrhythmias occur in approximately 10% of pregnancies in women with moderate to severe AS.<sup>14)46)</sup> The risk factors of complications are dependent on the functional status of the woman, the severity of obstruction and systolic function of the LV.<sup>14)</sup>

Data on pregnancy outcome of women with AS from reports of Silversides et al.<sup>46)</sup> and Hameed et al.<sup>47)</sup> are combined: 41 women with AS (29 mild-moderate, 32 severe AS) with 61 pregnancies in total. Heart failure was observed in 7 (11%), and arrhythmias in 2 (3%). These complications are higher in severe cases comparing with mild to moderate cases. There was 1 maternal death in severe cases. In fetus, there were 10 (16%) prematurity. Authors concluded that severe cases are high-risk for mortality and morbidity, and in women with > moderate AS, it is better to relieve before pregnancy if there are signs of decompensation, and better proceed with balloon valvuloplasty or surgery. When women become symptomatic during pregnancy and medical management fails, percutaneous balloon valvuloplasty can be performed as an emergency rescue.

**Coarctation of the aorta (COA) and aortopathy**

COA typically occurs distal to the origin of the left subclavian artery. It can be associated with other CHDs such as VSD and patent ductus arteriosus (so called coarctation complex), the most common of which is BAV. Most pregnant women with COA have undergone a surgical repair. There are a number of possible surgical repairs including the end-to-end anastomosis, subclavian flap repair, grafts interposition and stenting. Assessment should focus on the identification of residual lesions that can impact pregnancy risk including persistent hypertension, re-coarctation, aneurysms at the site of the repair especially in women with patch repair, aortopathy and aortic valve disease. Women with anatomically good repairs and no residual hypertension generally tolerate pregnancy well. The most common pregnancy complication is hypertension, which is seen in approximately 30% of pregnancies, but aortic dissection is rare.<sup>48)</sup> Beta-blocker (metoprolol or atenolol) is possibly effective for prevention of aortic root dilatation. Losartan use during pregnancy is not recommended due to its possible teratogenicity and induction of fetal kidney disease. Risk of infective endarteritis and endocarditis (high frequency association of BAV in women with COA) should be kept in mind even women with successful intervention.<sup>48)49)</sup> Beauchesne et al.<sup>48)</sup> reported 118 pregnancies in 50 women (30 repaired, 38% with significant residual COA [gradient  $\geq 20$  mmHg]), and these pregnancies resulted in 106 births. Thirty percent of them experienced hypertension during pregnancy and 1 early maternal death (Turner syndrome, due to aortic dissection), 11 miscarriages (9%) and 4 premature deliveries (3%). Authors concluded major cardiovascular complications were infrequent. However, systemic hypertension during pregnancy was common.

Several types of CHDs other than COA associated with aortic dilatation (aortopathy) in adults are as follows; BAV, TOF, single ventricle with pulmonary stenosis/atresia, truncus arteriosus, complete TGA and hypoplastic left heart syndrome. Histological abnormality of aortic wall, so called cystic medial necrosis, has been reported in these CHDs.<sup>6)50)</sup> Fortunately, there are no reports on dissection during pregnancy in these patients. Hereditary aortopathy such as Marfan, Ehlers-Danlos, Loeys-Dietz and Turner syndromes, etc. are not discussed here.

**Atrial septal defect (ASD) and atrioventricular septal defect (AVSD)**

ASD in childbearing age can be associated with RV dilation/dysfunction, and rarely, AF and PH. Isolated secundum ASD, repaired or unrepaired, are well tolerated during pregnancy unless PH is present. This is considered a low risk lesion with low rate of cardiovascular complications (1.3%).<sup>14)</sup>

Drenthen et al.<sup>51)</sup> reported 48 pregnancies in 26 women with balanced AVSD, and cardiovascular events were observed in 40% of completed pregnancy, and those were deterioration of NYHA class in 23%, worsening of pre-existing mitral regurgitation in 17%, arrhythmias in 19% and heart failure in 2%. CHD recurred in 6 (12%), 4 had AVSD, and 3 of them died including 2 LV hypoplasia. They concluded pregnancy is not always well tolerated in AVSD due to NYHA class deterioration and worsening of atrioventricular valve regurgitation. Offspring mortality is high. AVSD is a much more complex lesion with a higher pregnancy risk comparing with simple ASD.

**VSD**

Perimembranous VSD is most frequent in incidence internationally, but subpulmonary VSD is observed 25–30% in total patients with VSD in oriental countries.<sup>52)</sup> Significant VSD are associated with LV volume overload/dysfunction and PH. Small restrictive VSDs are

considered low-risk in the absence of PH. Subpulmonary VSD often associates with right coronary cusp prolapse and aortic regurgitation, and aortic regurgitation will persist after VSD and/or aortic valve repair. Large non-restrictive VSD are associated with PH/Eisenmenger syndrome and have significant risk during pregnancy. VSD associated with Eisenmenger syndrome is a different story as mentioned before. Cardiovascular events are rare (1.2%) in women with simple VSD even with residual mild aortic regurgitation.<sup>14)22)</sup>

## CARDIAC MONITORING OF THE MOTHER DURING PREGNANCY

Cardiovascular and respiratory changes in a normal pregnancy can mimic signs and symptoms of heart failure. Breathlessness, easy fatigability, a decrease in exercise tolerance, deep breathing and peripheral edema are common in normal pregnancy, therefore, it should be better not misunderstand as evidence of heart failure. Accurate evaluation of heart condition during pregnancy is thus recommended. When women with CHD become pregnant, attending cardiologists must explain the condition of CHD to obstetricians, and provide information on symptoms and physical change to be monitored during pregnancy and the perinatal period. In women with CHD, complications during pregnancy may often develop in the mother and fetus, and may sometimes be fatal. They must be continuously monitored by a team consisting of obstetricians, cardiologists, anesthesiologists, and nurses for cardiac complications such as arrhythmia, heart failure and thrombosis during pregnancy. Periodic checkups for healthy pregnant women by obstetricians generally consist of 3 checkups by 11 weeks of gestation, every 4 weeks monitoring in 10–12 to 20–23 weeks of gestation, every other week monitoring in 24 to 35 weeks of gestation, and weekly thereafter to the end of the 40th week. For women with moderate to high-risk CHD, cardiologists will checkup mother more closely; once at first visit (may be 5–8 weeks of gestation), and nearly 20 weeks, then follow at the same visit of obstetrician's schedule, if possible.<sup>1)2)53)</sup> For women with CHD, an appropriate monitoring schedule should be designed on the basis of healthy pregnant women according to the risk during pregnancy. In women with moderate to severe CHD, 2 weeks monitoring after 15 weeks of gestation and 1 week monitoring after 25 weeks of gestation are done. But when the condition of the mother or fetus do not become well, then mother is recommended to hospitalize after 20 weeks of gestation for rest, monitoring, and, in case, management.

## HEMODYNAMIC ASSESSMENT AND CARDIAC INVESTIGATIONS DURING PREGNANCY

It is preferable that patients with CHD are assessed for hemodynamic status several times during pregnancy and the puerperal period. Echocardiography, a noninvasive method providing detailed information, is very useful in evaluating hemodynamics during pregnancy.<sup>11)</sup> The first assessment should be conducted before pregnancy or during the first trimester when changes in hemodynamics are still slight. But pregnant women are often visiting outpatient clinic of cardiologists after becoming pregnant (5–8 weeks of gestation), so initial echo data will be obtained at that time. Patients with mild to moderate risk category should be evaluated for hemodynamics again during the late second trimester (26–28 weeks of gestation).<sup>11)</sup> Women with severe risk require more frequent hemodynamics assessment. When necessary, transoesophageal echocardiography is useful and also safe

in pregnancy. During the peripartum period, hemodynamics should be reassessed. Since childcare including breast-feeding may increase cardiac load, patients with severe CHD must be followed up until at least 6 months after childbirth for clinical course including hemodynamics.

Cardiac MRI is only required when the diagnosis of complex CHD or aortic pathology cannot be determined by echocardiography. Although cardiac MRI is believed useful for assessing right heart function and women with complex CHD, this technique must be limited for necessary cases since the risk of MRI to the fetus remains unclear.<sup>54)</sup> Cardiac catheterization and cardiac computed tomography should be limited to patients who may benefit from the examination as these techniques cause radiation exposure. Investigations that involve radiation exposure should not be withheld if indicated, following a discussion with the patient on risks and benefits of the test. In all cases, the radiation dose and duration of exposure should be minimized and the gravid uterus should be shielded. Since no increases in the risks of developmental retardation, central nervous system disorders and developmental disorders have been observed in children exposed to less than 100 mGy, exposure to radiation at this level is not considered to a valid reason for artificial termination of pregnancy.

While interpreting blood tests, normal pregnancy reference values must be used. Troponin is not normally increased in pregnancy and is the diagnostic test of choice to detect myocardial injury. A normal B-type natriuretic peptide level can be helpful to exclude cardiac decompensation.<sup>55)</sup>

## PSYCHOSOCIAL ISSUES

Psychosocial issues are also important during pregnancy and peripartum period. Anxiety and depression may be worsening during the perinatal period. Patients with CHD have strong desire to experience pregnancy and having a baby, and often feel anxious about the possible effect of pregnancy on their health and potential genetic risks to the child. In order to prevent depression and anxiety during pregnancy, patients should be provided with correct information and education on CHD, contraception, sexual activity and social support during the period of adolescence.

## ARRHYTHMIAS

The prevalence of arrhythmia in women with repaired CHD rises with age attributable to surgical scars, underlying substrate specific to each patient and aging. Some of these arrhythmias have a significant negative impact on life expectancy of women with CHD.<sup>56)</sup> New onset or increased frequency of preexisting arrhythmia can be observed during pregnancy due to maternal neural, hormonal, and physiological changes during the course of pregnancy in otherwise healthy pregnant women, however, majority of these arrhythmias are benign, and without clinical significance.<sup>57)58)</sup> While arrhythmias especially supraventricular tachyarrhythmia, ventricular tachycardia and high-grade atrioventricular block observed during pregnancy in women with CHD could cause significant hemodynamic compromise to both the mother and fetus. In spite of development of anti-arrhythmic treatment modalities, pharmacological agents used for the control of arrhythmia during pregnancy may have



potentially adverse effects on the mother and fetus.<sup>59)</sup> Data are very limited regarding the effects of anti-arrhythmic medications on the fetus. Most therapies have not been thoroughly tested in pregnancy, and virtually all drugs can cross the placenta. Majority of anti-arrhythmic drugs used are in United States Food and Drug Administration (FDA) category C (animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks). The risk/benefit ratio of anti-arrhythmic therapy during pregnancy in patients with CHD changes traditional concepts of management. Tachyarrhythmia can be associated with severe or even life-threatening symptoms in this condition. In considering therapy for cardiac arrhythmias or in sometimes for cardiac failure simultaneously, background hemodynamic substrate in each CHD is always be concerned. In general, immediate medical attention is indicated especially in women with CHD for arrhythmia such as supraventricular tachycardia or ventricular tachycardia that may severely affect the mother and fetus. In the series of Brodsky et al.,<sup>60)</sup> 2 patients with ventricular tachycardia during pregnancy died. In Japanese multicenter study,<sup>61)</sup> a patient with TOF associated with ventricular tachycardia during delivery was successfully recovered with administration of lidocaine. Two-thirds of supraventricular tachycardia was successfully administered anti-arrhythmic medication without maternal and fetal complication.<sup>61)</sup> Direct current cardioversion or catheter ablation was reported to be safe and effective during pregnancy.<sup>12)</sup> In patients with significant arrhythmias, pre-pregnant ablation should be performed, because in such cases, possibility of recurrent arrhythmias during pregnancy is highly expected.

When patients with brady-arrhythmias are suspected to be worsening during pregnancy, pacemaker implantation before pregnancy is recommended.<sup>62)</sup> Regarding catheter ablation or implantable cardioverter defibrillator (ICD) or pacemaker implantation during pregnancy, using echocardiography or 3D mapping system could reduce radiation exposure. Patients with implanted pacemaker (fixed rate atrial or ventricular pacing) or ICD before pregnancy tolerate pregnancy well.<sup>61)</sup>

## CARDIAC FAILURE

In women with CHD, cardiac failure happens after delivery is more common than during pregnancy. For example, small single center study in women with repaired TOF, have suggested that unfavorable RV remodeling persists even after delivery.<sup>42)63)</sup> Volume overload and tachycardia are the trigger of cardiac failure during pregnancy in women with CHD. Decreased systemic vascular resistance can induce low cardiac output with low peripheral perfusion, and may deteriorate the mother. LV end-diastolic pressure can be elevated due to excessive volume overload followed by elevated pulmonary artery hypertension and pulmonary edema. Then peripheral edema appear due to elevated venous pressure. Cardiac failure can induce maternal arrhythmias and death if that is severe. Also in such a case, fetus can be aborted or become low birth weight/premature infant. Therefore, women with NYHA class >III is advised not to be pregnant.<sup>64)</sup>

## THROMBOSIS

The management of patients with prosthetic valve, cyanotic CHD and Fontan, or other conditions those require anticoagulation (or antiplatelet agents) during late pregnancy

poses a therapeutic dilemma with risks to both the mother and fetus.<sup>1,2)</sup> Data regarding safety and limitations of warfarin, new oral anticoagulant direct-acting oral anticoagulants (DOACs) and heparin are limited, and controversy regarding best treatment option still exists. Pregnancy results in a hypercoagulable state especially in the late period of pregnancy due to increasing clotting factor concentration and platelet adhesiveness, and a reduction in the degree of fibrinolysis and protein S activity. Therefore, these coagulation changes result in an increased risk of thrombosis and embolism during pregnancy and after delivery. Leg care preventing deep vein thrombosis is important during pregnancy and immediately after delivery (especially after Caesarean section), and is useful prevention for thromboembolism especially in women with moderate to severe CHD, in those, femoral vein has been sometimes occluded due to long standing femoral catheter insertion in perioperative period during neonate and infant. Especially in Fontan patients, leg care is most important.

## DRUG THERAPY DURING PREGNANCY

Drugs used for pregnant women must be selected after careful consideration of the risk-benefit balance in the mother and fetus. The adverse effects of drugs on fetus are classified into teratogenicity effects and fetal toxicity. Many drugs are substantially excreted in the breast milk, however, the blood concentration of a drug given to the mother is substantially lower than the therapeutic range of the drug in the neonate. The pregnancy category proposed by the FDA of the United States is often referred to as important information on the risk of drugs to the fetus or neonate.<sup>1)</sup> When drugs contraindicated for pregnant women in the package inserts or drugs not accepted by the National Health Insurance (NHI) are prescribed, the physicians must fully explain the risks and benefits of such drugs to the patients and their families and obtain informed consent.

Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are contraindicated for women throughout pregnancy since they may have teratogenicity to the fetus and directly affect the kidney of the fetus and neonate to cause renal failure, abortion or stillbirth.<sup>65)66)</sup> Amiodarone is basically contraindicated for pregnant women since it may cause abnormal thyroid function in the fetus. Bosentan is absolutely contraindicated for pregnant women in the FDA's recommendation. Warfarin has teratogenicity when given during the first trimester, and increases the risk for bleeding disorders in the fetus and neonate. Heparin does not have fetal toxicity because it does not cross the placenta, while the incidence of thrombosis among patients receiving heparin is higher than those receiving warfarin. Low-dose aspirin therapy is rated pregnancy category C by the FDA's recommendation and believed relatively safe. However, "Aspirin is contraindicated for women in the last 12 weeks of gestation (regardless of the dose)" by the Drug in Japan in the package insert; physicians must fully explain the risks and benefits of low-dose aspirin therapy during the second and third trimester of pregnancy to obtain consent from the patient.<sup>2)</sup>

Meticulous prophylaxis for deep venous thrombosis, including early ambulation and compression stockings, can be useful for all patients with intracardiac right to left shunting. Subcutaneous or low-molecular weight heparin is reasonable for prolonged bed rest. Full anticoagulation can be useful for the high-risk patient. There is no evidence of teratogenicity in DOACs, but these medications are not effective for prevention of thrombosis in mechanical valve.

## CARE FACILITY FOR PREGNANCY (TEAM APPROACH)

Women with CHD in whom pregnancy poses a risk must be carefully monitored and planned for safer pregnancy and childbirth. High-risk pregnancy should be monitored in tertiary care facility in which team approach by obstetricians, heart disease specialists (cardiologists, pediatric cardiologists, adult CHD specialists, and cardiovascular surgeons), anesthesiologists, neonatologists, and nurses who have knowledge and experience in the management of high-risk pregnancy have been established.<sup>2)3)</sup> Every tertiary care facility in which pregnancy and childbirth in women with CHD are managed should establish such a specialist team. Hospitals where such team cannot be established within the institutions should build a system to facilitate consultation with CHD specialists in other hospitals.

## INVASIVE TREATMENT DURING PREGNANCY

It has been reported that intervention using balloon catheters during pregnancy is effective for patients with pulmonary, aortic or mitral stenosis.<sup>67)68)</sup> But usually, these interventions are thought to be a kind of emergency rescue. So, the indication of intervention is different from those during not pregnant. Indication of intervention should be severe cardiac failure with life threatening to both the mother and fetus. In case with pulmonary stenosis, symptoms due to pulmonary stenosis plus at least mean pressure gradient between pulmonary artery and RV systolic pressure >50 mmHg or RV systolic pressure >75 mmHg, and in case with AS, mean pressure gradient between aorta and LV systolic pressure >50 mmHg or aortic orifice size under 0.6 cm<sup>2</sup>/m<sup>2</sup> are indications of intervention. In cases with AS, care must be taken not to induce secondary severe aortic regurgitation. In case with mitral stenosis, intervention is considered if symptoms of pulmonary congestion or AF develop.<sup>2)</sup>

It is important to reconsider whether symptoms of the mother are exactly due to stenotic lesion itself or not. Intervention should be performed after the period of fetal organogenesis (13–14 weeks of gestation) or after 18 weeks of gestation. Protection from radiation exposure is necessary for the fetus. In patients with COA, balloon dilatation with stent is preferred method of choice, because aortic wall is intrinsically fragile during pregnancy. In cases those experienced catheter intervention during pregnancy, surgical procedure will be often followed after delivery.

The management of gravida who require cardiopulmonary bypass poses problems that are difficult to solve. The fetus is at greatest risk in early in the pregnancy, whereas the mother is at greatest risk in later in the pregnancy. Cardiovascular surgery is rarely required during pregnancy, but it can be necessary in some cases.<sup>2)</sup> The indication of emergency cardiovascular surgery in women with AS during pregnancy should be determined; timing of worsening of valvular regurgitation or existence of progressive heart failure; status of aortic aneurysms with impending aortic dissection or the status of vegetation or worsening of heart failure with infective endocarditis, or other life threatening conditions. When surgery during pregnancy is unavoidable, it should be performed at 16 to 20 weeks of gestation, or surgery at 24 to 28 weeks of gestation or thereafter are safer to the fetus than in the other periods. When surgery could be waited to 28 to 30 weeks of gestation or thereafter, surgery after childbirth may be feasible.<sup>69)70)</sup> Cardiovascular surgery with cardiopulmonary bypass during pregnancy is very risky for the mother and fetus. For protection of low perfusion during bypass, high blood flow and relatively high pressure is inevitable. Fetal mortality is reported to be

9–30%.<sup>71)</sup> On the other hand, mortality of the mother is low comparing with the fetus, but complication rate of the mother is high. Therefore, it is better to avoid cardiovascular surgery during pregnancy.

## INFECTIVE ENDOCARDITIS PROPHYLAXIS DURING PREGNANCY AND DELIVERY

The guidelines for the prevention and treatment of infective endocarditis<sup>72)</sup> recommend that the prevention of infective endocarditis is considered for most patients with CHD (**Table 4**). The common sources of bacteremia are oral procedures, urogenital infection, delivery, childbirth, indwelling catheter and surgeries. Bacteremia may develop after spontaneous abortion, vaginal delivery assisted by episiotomy or Caesarean section, among others. Antibiotic treatment of infective endocarditis should be performed in a fashion similar to that for non-pregnant patients according to the susceptibility of causative agents. Preventive administration of antimicrobial agents during delivery is recommended for patients with a risk for infective endocarditis.<sup>73-75)</sup> There is no consensus at this point of time for the preventive administration of antimicrobial agents in women with CHD during delivery.

## CONTRACEPTION

Contraception in women with severe CHD should be maximum efficacy because the contraceptive failure can be fatal. There is lesion-specific contraception.<sup>71)76-78)</sup> Unfortunately, many women with CHD do not have adequate knowledge of safe contraception options.<sup>76-79)</sup> Estrogen-containing preparations are associated with thromboembolic risks and are contraindicated in women with cardiac conditions who are high-risk for thromboembolic complications. This includes women with mechanical valves, Eisenmenger syndrome and Fontan circulation. Progesterone-only pills are safer for women with these conditions but have high failure rates, and therefore are not suggested when prevention of pregnancy is crucial. Non-oral progesterone-only contraception such as progesterone implants has very low failure rates and can be used in most conditions. Progestogen-loaded intrauterine devices such as Mirena are the most efficacious forms of contraception and are also safe choices for many women with significant CHD, but can be associated with vagal responses at the time of insertion, which is a potentially serious complication for women with pulmonary vascular disease or Fontan circulation. Barrier methods have high failure rates and are not advised when pregnancy risk is high and prevention of pregnancy is important. Tubal sterilization is a permanent surgical method of contraception, however the procedure carries a risk for some women with complex CHD such as those with Eisenmenger syndrome.

**Table 4.** Patients with CHDs recommended to receive preventive antimicrobial treatment during delivery

### Obstetric operations/procedures and delivery

- Women with a history of infective endocarditis
- Women with CHD other than ASD/complete repair of PDA, ASD, and VSD
  - Women with cyanotic CHD
  - Women who underwent repair using artificial patches and devices within the last 6 months
  - Women who underwent repair and have residual shunts around the implanted artificial patches and devices
- Women using artificial valves

ASD = atrial septal defect; CHD = congenital heart disease; PDA = patent ductus arteriosus; VSD = ventricular septal defect.

## INFERTILITY AND ASSISTED REPRODUCTIVE TECHNOLOGIES

If pregnancy is not advised on medical reasons, alternative options such as surrogate motherhood or adoption child may be considered. For women in whom pregnancy is considered safe, it is important to ensure that fertility medications and techniques are generally safe for women with CHD. Maternal and fetal risks are increased in those receiving assisted reproductive therapies.<sup>80)</sup> For women at risk for thromboembolic complications, gonadotropins should be used with caution as they increase estrogen levels, therefore potentially increasing risk. For some women with high-risk cardiac conditions such as a Fontan circulation, complications of fertility therapy could result in serious cardiac compromise such as hypotension and/or bradycardia, therefore modifications in protocols may be required to prevent this complication.

## PERIPARTUM CARE, DELIVERY METHODS, AND CARING FOR BABY

With few exceptions, vaginal delivery is preferred over Caesarean section as it carries lower risks for both the mother and fetus due to smaller shifts in blood volume, less hemorrhage, fewer clotting complications, and fewer infections.<sup>81)</sup> Modifications that may help to diminish the cardiovascular stress at the time of labor include good pain management epidural analgesia and laboring in the left lateral position. For those with a Fontan circulation, avoidance of excessive maternal effort by assisting the active second stage of labor may be helpful.<sup>82)</sup> Non-invasive monitoring such as oximetry and telemetry can be used to monitor women at risk for decompensation during labor and delivery. Invasive cardiac monitoring is rarely required. Oxytocin for the management of the third stage of labor is best given as a continuous intravenous infusion to avoid the risks of peripheral vasodilation, tachycardia and fluid retention that could be potentially life threatening in patients with low cardiac output or left-sided obstructive lesions.<sup>83)</sup>

Caring for baby is a very hard job for women with CHD after delivery, because they have decreased cardiac function due to drastic hemodynamic burden during delivery. In women with CHD, recovery of hemodynamics and cardiac function takes longer time (4–6 months after delivery) than those with normal heart (1 month after delivery). Breastfeeding is a good way, but it makes mother become tired and exhausted if baby sucks mother's milk so frequently as every 3 hours or more. In women with moderate to severe CHD, mixed feeding is better than breastfeeding only. So mixed feeding, breast and artificial feeding, is proper for those with CHD more than moderate severity. Also, it is better to help her by somebody, preferably by her real mother.

## IMPACT OF PREGNANCY ON CARDIAC CONDITIONS LONG-TERM AFTER DELIVERY

Few data exist regard to the impact of pregnancy on long-term outcomes in women with CHD.<sup>84-86)</sup>

### Bioprosthetic valves

It is recognized that bioprosthetic valves degenerate at a rapid rate in women with childbearing age,<sup>87)</sup> but there is an emerging consensus supported by a number of studies that

pregnancy itself might not hasten that process.<sup>88)</sup> Thus, whether there is a long-term negative effect of pregnancy on bioprosthetic valves or not still remains controversial.

### Aortopathy

Whether pregnancy causes further aortic dilatation in women who already have a dilated aorta is unknown, but estrogen has been shown to inhibit collagen and elastin deposition in the aorta. It has been reported that pregnancy may be accompanied by fragmentation of elastic fibers.<sup>6)</sup> Whether these gestational changes in the aorta are additive to the underlying histologically abnormality is also unknown. Donnelly et al.<sup>89)</sup> reported long-term results of 199 pregnancies in 69 women with Marfan syndrome and they found aortic growth rate during pregnancy (median 3 mm) was higher comparing with matched controls (non-pregnant Marfan syndrome). Also, there was increase in the base line diameter from 35 to 43 mm in the pregnant group compared with an increase from 36 to 37 mm in the matched controls (non-pregnant Marfan syndrome) over a mean follow-up period of 5.6 and 7.7 years, respectively. There is a low incidence of aortic complications during pregnancy in women with Marfan syndrome and an aortic diameter <4.5 cm. However, pregnancy does increase the risk of aortic complications in the long-term in this group of patients.

### Systemic right ventricle

Systemic RV function and tricuspid regurgitation in TGA post atrial switch operation is getting worse during pregnancy and/or immediately after delivery, and those progress even long-term after delivery or no recovery happens in some patients.<sup>30)</sup> Metz et al.<sup>90)</sup> reported there were 21 pregnancies in 25 women with TGA after atrial switch operation, and serial echocardiographic data demonstrated a fall in RV function during pregnancy, with some improvement postpartum. Zentner et al.<sup>91)</sup> reported that in women with TGA post atrial switch operation, the long-term occurrence of sudden cardiac death and clinical heart failure medication or hospitalization was more frequent in women who experienced pregnancy compared with non-pregnant women during 5 years follow-up. Pregnancy may have an adverse effect on long-term outcomes in women with systemic right ventricles. Also, Bowater et al.<sup>92)</sup> collected 31 pregnancies in 18 women with TGA post atrial switch operation and found that the mean NYHA class deteriorated from 1 prior pregnancy to 1.4 during pregnancy. At 1-year follow-up, the RV function did demonstrate significant deterioration with no deterioration in the control group. However, at 51 months follow-up results were similar compared with controls. They concluded pregnancy is associated with a premature deterioration in RV function in women with a systemic right ventricle. These women are also more symptomatic, with a greater reduction in functional class compared with patients with a systemic right ventricle who do not undergo pregnancy.

### TOF

Kamiya et al.<sup>42)</sup> reported that a series of 40 deliveries in 25 women showed that RV dilatation tends not to recover at 6 months after delivery and progress and more dilated with each subsequent pregnancy (after the second and third pregnancies). Uebing et al.<sup>93)</sup> reported that there was a persistent increase in RV size, but no decrease in RV function in women with repaired TOF who became pregnant during the mean follow-up of 2.9 years. Also, Assenza et al.<sup>63)</sup> reported long-term effects of pregnancy on RV remodeling in women with repaired TOF using MRI, and found that RV end-diastolic volume significantly increased in these pregnant comparing with those not pregnant at the mean follow-up of 41 months. Women with repaired TOF who have completed pregnancy appeared to experience an accelerated rate of RV remodeling, defined as an increase in end-diastolic volume. From these reports, pregnancy in women with repaired TOF is associated with a persisting increase in subpulmonary ventricular size.



In women with complex CHD, progression and deterioration of functional changes during pregnancy and postpartum could happen. These changes may be attributable to the longevity pattern of the CHD. There are many uncertainties about longevity patterns in women with CHD after deliver a baby since only small studies have been published. Future large prospective multicenter randomized trials are necessary to solve these important problems, and these studies will surely contribute to proper pre-pregnant counseling in the future.

## CONCLUSIONS AND STATEMENTS

The outcome of pregnancy and delivery is favorable in most women with CHD provided that functional class and systemic ventricular function are good. Comparing with other structured heart diseases, CHDs represent the most common cause of maternal morbidity. Better assessment and management of this group of patients is likely to make a substantial improvement in outcomes for the mother and fetus. There is a small group of patients with complex CHD or high-risk CHD in whom pregnancy is either dangerous or contraindicated owing to the very high-risk to the mother and fetus. If pregnancy occurs and continues with these patients, they should be managed and delivered in specialized centers with multidisciplinary expertise. A painless vaginal delivery or an assisted delivery is usually feasible and is preferable for women with CHD especially more than moderate severity.

Medications should be used only when necessary in any pregnant women with CHD. Certain medications are contraindicated during pregnancy, therefore, those should be discontinued before pregnancy or early during pregnancy. Although infective endocarditis is a recognized risk for maternal morbidity and mortality, endocarditis prophylaxis around the time of delivery is recommended for most women with CHD. Breast-feeding is feasible in most women with CHD, however, women requiring cardiovascular medications should be aware that many of the medications will cross into breast milk and should clarify the potential effect of medications on the infant with a pediatrician. In women with complex CHD, progression and deterioration of functional changes during pregnancy and postpartum may be attributable to the longevity pattern of the CHD.

In management of women with CHD and pregnancy, following items are mandatory: 1) counseling and risk assessment; 2) preconception medication and surgical adjustments, catheter intervention, arrhythmia ablation, or reparative surgery if feasible; 3) maternal and fetal monitoring including fetal echocardiography; 4) planning for labor and delivery, in women with more than moderate CHD, multidisciplinary approach is preferable; and 5) cardiac monitoring and follow-up after post-partum period.

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