Maternal and Fetal Cardiovascular Disease

Tomoaki Ikeda
Chizuko Aoki-Kamiya
Editors

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Preface

The advance in medical and surgical treatments for congenital heart disease has allowed many women with congenital heart disease to reach adulthood with less limitation of motility. Inherited diseases, such as channelopathies and heritable connective tissue disorders, have been able to be diagnosed in youth by genetic tests. Social background and reproductive medicine have raised the maternal age. Therefore, the number of pregnancies complicated with cardiovascular disease has been increasing. The time when women with cardiovascular disease were discouraged across the board from becoming pregnant has passed. At this time, medical practice by which they can give birth more safely is needed.

The circulation state changes dynamically throughout pregnancy and childbirth. While many women with a cardiovascular disease give birth safely, in some critical conditions, a pregnancy becomes a high-risk event which threatens the lives of mother and fetus. As a practical matter, cardiovascular disease is one of the leading causes of maternal death in Japan. Therefore, acquiring knowledge and skills in this field is quite important.

This book, entitled *Maternal and Fetal Cardiovascular Disease*, covers many issues concerning pregnancy and fetuses complicated by cardiovascular disease. In Chaps. 1–4, the general theory for follow-up of pregnancies with cardiovascular disease in antepartum, intrapartum, and postpartum is introduced. Especially, obstetric anesthesia in women with cardiovascular disease is explained in Chap. 3. Preconception approach and prophylaxis for infective endocarditis are mainly described in Chaps. 5–7. Chapter 8 focuses on the most severe complication, maternal death in Japan. Chapters 9–16 deal with the details of clinical features and prognosis concerning major cardiovascular diseases, especially based on previous reports, including those in the Japanese population. Lastly, fetal cardiology is reviewed in Chaps. 17 and 18.

A multidisciplinary team, which is composed of trained obstetricians, adult and pediatric cardiologists, anesthesiologists, midwives, and other specialists involved, is necessary for the management of mothers and fetuses with high-risk cardiovascular disease. We hope that this book will provide physicians, nurses, and comedical workers with invaluable knowledge of this field and help to achieve safer medical care for mothers and fetuses.

We deeply appreciate the doctors who contributed great work in the process of writing this book and pay respect to many doctors and health-care professionals

who contributed to this field. Pregnancy and delivery are one of the life choices for all women. It is our fervent hope that this book will help as many women with cardiovascular disease as possible to live their own lives, as they choose.

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Antepartum Management of Women with Cardiovascular Disease

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Koichiro Niwa

Abstract

Cardiac disease is a major cause of maternal death. The number of such cardiac patients at risk is expected to grow. Women with pulmonary hypertension, severe left ventricular outflow stenosis, cyanotic congenital heart disease, aortic root dilatation, cardiac dysfunction, and mechanical valves have a high risk. The most frequent complications during pregnancy and delivery are heart failure and arrhythmias. Risk stratification for pregnancy and heart disease relates to the functional status of the patient and is lesion specific. Timely prepregnancy counseling should be offered to all women with heart disease in order to prevent avoidable pregnancy-related risks. Adequate care during pregnancy, delivery, and the postpartum period requires a multidisciplinary team approach with cardiologists, obstetricians, and anesthesiologists and other related disciplines. Successful pregnancy is feasible for most women with heart disease with a relatively low risk when appropriate counseling and optimal care are provided.

Keywords

Cardiovascular disease · Adult congenital heart disease · Congenital heart disease
Cardiac failure · Arrhythmia

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1.1 Introduction

Successful pregnancy is feasible for most women with heart disease (HD) when appropriate counseling and optimal care are provided. However, complications, such as heart failure and/or arrhythmia, can occur throughout pregnancy, delivery, and the postpartum period in women with moderate to severe heart disease, but most of these complications can be managed. Women with pulmonary hypertension, severe left ventricular outflow stenosis, cyanotic congenital heart disease, aortic root dilatation, cardiac dysfunction, Fontan procedure, Kawasaki disease with coronary artery lesions, and mechanical valve are at high risk for both the mother and the fetus (Table 1.1) [1, 2].

Advances in medical and surgical treatments have led to more than 90% of children with congenital heart disease (CHD) surviving into adulthood. Most interventions, however, are not curative, and many adults with CHD face the prospect of further surgery, cardiac failure, and arrhythmia. The burden of pregnancy and delivery represents a new challenge for women with HD (Fig. 1.1).

While many women with HD tolerate the hemodynamic changes of pregnancy, others may face significant immediate or late risks of pregnancy, including volume overload, arrhythmias, progressive cardiac dysfunction, and death (Fig. 1.2). Management of complications is firstly through rest, followed by medication, intervention (catheter or surgery), and termination, if fetus is growing enough, especially after 28 or 30 weeks gestation. Women with HD who would be expected to develop heart failure during pregnancy and delivery should be treated before becoming pregnant, when feasible. Women with significant arrhythmias that could induce hemodynamic compromise during pregnancy should be ablated before pregnancy. Management and prophylaxis of infective endocarditis are also mandatory. Leg care is the most important preventive measure for thromboembolism, especially in patients with moderate to severe CHD, in whom the femoral vein has been sometimes occluded due to long-standing femoral catheter insertion during the perioperative period as neonates and infants. Complications of the fetus include growth failure, abortion and stillbirth, and retinal and lung complications due to immaturity (Fig. 1.2).

Table 1.1 Patients with heart diseases requiring careful monitoring during pregnancy or who are strongly recommended to avoid pregnancy

• Pulmonary hypertension (Eisenmenger syndrome)
• Left ventricular outflow or inflow tract stenosis (severe aortic stenosis with a mean pressure of >40–50 mmHg)
• Heart failure (NYHA Class III–IV, left ventricular ejection fraction <35–40%)
• Marfan syndrome (ascending aortic diameter at end-diastole >40 mm)
• Mechanical valves
• Cyanotic heart disease (arterial oxygen saturation <85%)
• Fontan procedure
• Kawasaki disease with coronary artery aneurysm and stenosis
• Arrhythmias those induce hemodynamic compromise

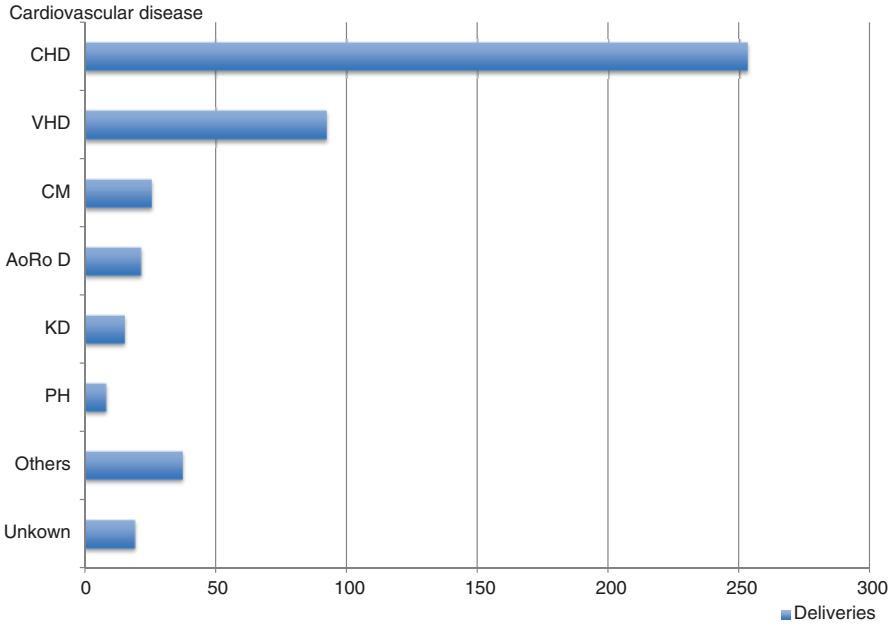

Fig. 1.1 Incidence of structured heart disease in pregnancy. In 138 departments of obstetrics in Japan, 80,455 pregnancies occurred during 2002–2003; 769 of them (0.96%) were from women with cardiovascular disease. Of these, 470 (0.58%) were structural heart disease, and congenital heart disease is the most frequent with 245 of 470 (=52.1%). *CHD* congenital heart disease, *VHD* valvular heart disease, *CM* cardiomyopathy, *AoRo D* aortic root disease, *KD* Kawasaki disease, *PH* pulmonary hypertension. Modified from Niwa K. Circ J 2005; 69: 110

Fig. 1.2 Risk of pregnancy in women with CHD

- Maternal risk
  - Maternal death
  - Other potential complications to consider *(than death):*
    - » Stroke/Arrhythmia
    - » Overt Heart Failure
    - » Adverse effect on cardiovascular function and thus, prognosis
- Fetal risk
- Recurrence of CHD
- Preterm delivery/IUGR/embryopathy/intracranial
- bleeding/lactation

1.2 Cardiovascular and Other Physiological Changes During Pregnancy and Delivery (Tables 1.2 and 1.3, Fig. 1.3)

In the first trimester, the arterial pulse is characterized by a rapid rise. The jugular venous pulse becomes more conspicuous, especially after 20 weeks' gestation. The first heart sound is louder with a widely splitting second heart sound. Pulmonary systolic murmur is common because of the augmented volume load and increased heart rate.

Table 1.2 Hemodynamic changes during pregnancy, labor, and delivery

During pregnancy
Cardiac output increase by 60–80%
Blood volume increase by 40–50% increase
During labor and delivery
Increase in blood volume with uterine contraction (300–500 mL)
Increase in venous return
Total amount of blood loss during delivery is 400–500 mL (vaginary) and 800–900 mL (C section)

Table 1.3 Changes during pregnancy – other than hemodynamics

1, Hematological: hypercoagulable state, anemia
2, Respiratory change: increased tidal volume
3, Aortic wall: fragmentation of medial elastic fiber
4, Autonomic nervous system: increase HR by 20%
5, Hormonal: increased cortisol, estrogen, and renin-angiotensin-aldosterone

Fig. 1.3 Hematologic changes during pregnancy

1, Major changes in hemodynamics, hormones, cathecolamine, 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, arrhythmogenecity

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

1.2.1 Hemodynamic Changes (Fig. 1.4)

Hemodynamics during pregnancy and delivery is significantly affected by changes in fluid circulation, hematology, respiratory function, endocrinology, and the autonomic nervous system [2, 3]. Plasma volume begins to increase from 4 weeks' gestation, peaks at 32 weeks' gestation, and is then maintained at a similar level or increases gradually to a volume 40–50% higher than before pregnancy [4, 5]. The heart rate peaks at around 32 weeks' gestation to about 20% greater than before pregnancy. The tidal volume increases by 18–25%, and cardiac output increases to 30–50% greater than before pregnancy at 20–24 weeks' gestation, and is maintained at a similar level throughout the pregnancy [5]. Meanwhile the aortic pressure and systemic vascular resistance decrease during pregnancy. In late pregnancy, low blood pressure can occur due to compression of the inferior vena cava by the enlarged uterus, especially in the right decubitus position or lying on the back. The pulmonary pressure remains similar throughout pregnancy because of increased pulmonary blood volume with decreased pulmonary vascular resistance. Cardiac function throughout pregnancy is affected by these changes of preload and afterload.

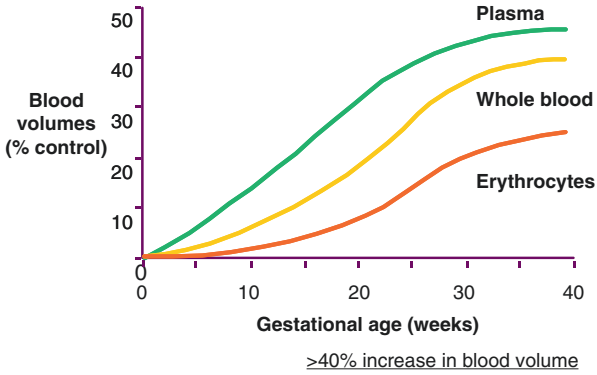

Fig. 1.4 Possible factors affecting outcome pregnancy in CHD

During delivery, hemodynamics are influenced by the posture of the body, mode of delivery, labor, and type of anesthesia. Uterine contraction and labor pain increase the circulatory volume by 300–500 mL, cardiac output by 15–25%, and heart rate and blood pressure [2, 3]. It is preferable that women in labor be maintained in the left decubitus position, because the uterus compresses the inferior vena cava and abdominal aorta when lying on the back. Typical blood loss during vaginal delivery is 400–500 mL, compared with 800–900 mL during cesarean section. This blood loss, labor, and pain could induce rapid hemodynamic change. Therefore, a painless vaginal delivery is the preferred approach for women with moderate to severe HD or women with NYHA>II. Immediately after delivery, the venous return increases abruptly after the pressure on the inferior vena cava from the enlarged uterus has been alleviated. These drastic hemodynamic changes could have a negative influence on cardiac function and induce cardiac dysfunction or cardiac failure. Heart rate, blood pressure, and cardiac output typically return rapidly to normal during the postpartum period. In women with heart disease, recovery of hemodynamics and cardiac function takes longer (4–6 months after delivery) than normal delivery [2, 3]. In high-risk pregnancies, women with originally low cardiac function, this cardiac dysfunction perpetuates for much longer than those with normal hearts or mild HD and sometimes may not recover to the prepregnant status.

1.2.2 Hematological Changes: Hypercoagulable State, Anemia

Red blood cell counts increase by 20–30% along with increased production of erythropoietin. However, relative anemia occurs, due to the increased plasma volume during pregnancy. White blood cell counts increase up to 13,000/mm, particularly neutrophils [2, 3]. Platelet counts decrease slightly. In late pregnancy, anticoagulant factors, such as plasma fibrinogen, von Willebrand factor, and coagulation factors I, V, VII, VIII, X, and XII, as well as 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 state, meticulous care must be taken for women with mechanical valves, Kawasaki

disease with coronary artery aneurysm or atrial fibrillation, and those prone toward deep vein thrombosis. During the first and second trimesters, hemoglobin and hematocrit levels decrease, which leads to a relative anemia [2, 3]. In severe cases, ferrous supplementation therapy becomes necessary.

1.2.3 Respiratory Change

Respiratory physiology is altered early in pregnancy because of chemically induced hyperventilation, due to increased progesterone levels. While the minute ventilation (45% increase) and intake volume are increased, the vital capacity remains stable, and the residual volume decreases by 40% [1]. Later in pregnancy, lung volume reserve decreases due to elevation of the diaphragm, and then, breathlessness becomes common, even in normal pregnancies.

1.2.4 Great Arterial Wall

The fragility of the arterial wall increases during pregnancy, due to increased production of estrogen, which has been considered responsible for interference with collagen turnover, in conjunction with relatively decreased elastic fiber, and leads to fragmentation of the elastic lamella. Increases in serum relaxin levels during pregnancy cause a decrease in collagen synthesis. The so-called cystic medial necrosis (fragmentation of medial elastic fiber) in the aorta is observed normally during pregnancy and increases aortic diameter and stiffness. This is an adaptive response to the increased blood volume. Since the aortic wall becomes more fragile during pregnancy, aortic dissection may occur in susceptible patients, such as Marfan syndrome associated with dilated aorta [6, 7].

1.2.5 Autonomic Nervous System

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

1.2.6 Hormonal Change

Increases in cortisol, estrogen, and renin-angiotensin-aldosterone (RAAS) occur during pregnancy. However, the relationship between hormonal and hemodynamic changes remains unclear.

1.3 Cardiac Assessment Before Pregnancy

It is important for women with HD to undergo appropriate assessment of pulmonary artery pressure, ventricular function, aortic diameter, cyanosis, New York Heart Association (NYHA) classification, cardiopulmonary exercise test, and other factors or appropriate examinations in order to predict the risk of pregnancy-related complications in the mother and fetus. Prepregnancy checkup for patients with underlying HD includes history taking, physical examination, chest X-ray, electrocardiogram (ECG), and echocardiography. Cardiac catheterization, exercise stress test [9], and Holter monitoring may be also conducted whenever necessary.

1.4 Prepregnancy Counseling

Women with HD should receive prepregnancy counseling, including discussion about the risk to the mother and fetus, hereditary risk, possible course of pregnancy, sexual activity, and caring for the baby [1–3]. It is likely that women with HD will experience heart failure and/or arrhythmia during pregnancy and after delivery and encounter difficulties in caring for the 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 for their individual patients. Table 1.1 lists the patients with HD and conditions that require careful monitoring during pregnancy or should be advised to avoid pregnancy. This HD is high risk for both the mother and fetus and can develop cardiac failure, arrhythmias, thromboembolism, aortic dissection, or increase cyanosis. Women with Eisenmenger syndrome, severe left ventricular outflow tract stenosis, cardiac failure (NYHA III–IV with left ventricular ejection fraction <35%), and aortic root dilatation (Marfan syndrome with aortic root size >45 mm, bicuspid aortic valve with aortic root size >50 mm) should possibly avoid pregnancy or terminate pregnancy, or become pregnant after surgical repair if possible (Table 1.1). Among high-risk patients, termination and delivery could be considered after 28–30 weeks' gestation when the maternal or fetal condition deteriorates rapidly (See Chap. 5).

1.5 Cardiac Monitoring of the Mother During Pregnancy

Cardiovascular and respiratory changes in a normal pregnancy can mimic the signs and symptoms of HD. Breathlessness, easy fatigability, decreased exercise tolerance, deep breathing, and peripheral edema are common in normal pregnancy. Therefore, it should be better to not misinterpret these signs as evidence of HD. Accurate evaluation of heart conditions during pregnancy is thus recommended.

When women with HD become pregnant, attending cardiologists must explain the condition of HD to the obstetricians and provide information on the symptoms and physical changes to be monitored throughout the pregnancy and the perinatal

period. In women with HD, complications during pregnancy may often develop in the mother and the fetus and may sometimes be fatal. They must be monitored continuously by a team consisting of obstetricians, cardiologists, anesthesiologists, and nurses for cardiac complications, such as arrhythmia, heart failure, and thrombosis, throughout the pregnancy. Periodic checkups for healthy pregnant women by obstetricians generally consist of three checkups by 11 weeks' gestation, monitoring every 4 weeks at 10–12 to 20–23 weeks' gestation, every other week monitoring for 24–35 weeks' gestation, and weekly thereafter, to the end of the 40th week. For women with HD, moderate to high risk, cardiologists will check up on the mother more closely, once at first visit (~5–8 weeks' gestation) and at ~20 weeks; then follow the same visit as the obstetricians schedule, as possible [1, 2]. In women with HD, an appropriate monitoring should be designed according to the maternal risk during. In pregnant women with moderate to severe HD, biweekly consultation after 15 weeks' gestation and weekly consultation after 25 weeks' gestation could be performed. However, when the condition of the mother or fetus is not well, the mother should be hospitalized after 20 weeks' gestation for rest, monitoring, and management.

1.6 Hemodynamic Assessment During Pregnancy

It is preferable that patients with HD should be assessed for hemodynamic status several times throughout the pregnancy and the puerperal period. Echocardiography is a noninvasive method that provides detailed information, which is very useful in evaluating hemodynamics during pregnancy [10]. The first assessment should be conducted before pregnancy or during the first trimester when changes in hemodynamics are still minimal. However, pregnant women often visit cardiology outpatient clinics after becoming pregnant (5–8 weeks' gestation), so initial echo data will typically be obtained at that time.

Patients with mild to moderate risk should be evaluated for hemodynamics again during the late second trimester (26–28 weeks' gestation) [11]. Patients with severe risk require more frequent hemodynamics assessments. Hemodynamics should also be reassessed during the peripartum period. Since childcare including breast-feeding may increase cardiac load, patients with severe HD must be followed up until at least 6 months after childbirth for the clinical course, including hemodynamics.

Although cardiac MRI is believed to be useful in assessing right heart function and in patients with complex CHD, this technique must be limited to essential cases, since the risk to the fetus remains unclear [12]. Cardiac catheterization and cardiac CT should be limited to patients who may benefit from the examination as these techniques involve radiation exposure. 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 be a valid reason for artificial termination of a pregnancy (see Chap. 6).

1.7 Psychosocial Issues

Psychosocial issues are also important during pregnancy and delivery. Anxiety and depression may worsen during the perinatal period. Patients with HD have a strong desire to experience pregnancy and to have 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 accurate information and education on HD, contraception, sexual activity, and social support during adolescence.

1.8 Arrhythmias

Recently, it has become more common for patients with CHD to reach childbearing age. The prevalence of arrhythmia in treated CHD patients increases with age, due to surgical scars, underlying substrate specific to each patient and aging. Some of these arrhythmias have significant negative impacts on the life expectancy of patients with CHD [13, 14]. New onset or increased frequency of preexisting arrhythmias can be observed during pregnancy due to maternal neural, hormonal, and physiological changes throughout the course of pregnancy in otherwise healthy pregnant women. However, the majority of these arrhythmias are benign and are without clinical significance [15]. Meanwhile arrhythmias, especially supraventricular tachyarrhythmia (SVT), ventricular tachycardia (VT), and highgrade atrioventricular block in pregnant women with HD could cause significant hemodynamic compromise to both the mother and fetus. Despite the development of anti-arrhythmic treatment modalities, pharmacological agents used for the control of arrhythmia during pregnancy may have adverse effects on the mother and fetus [16]. 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. The majority of anti-arrhythmic drugs used are in the US 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 HD changes the 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 sometimes for cardiac failure simultaneously, the background hemodynamic substrate for each HD should always be considered. In general, immediate medical attention is indicated, especially in women with HD for arrhythmia, such as SVT or VT, which may severely affect both the mother and fetus. In the series of reports by Brodsky [17], two patients with VT during pregnancy died. In a Japanese study [18], a patient with tetralogy of Fallot associated with VT during delivery recovered successfully following administration of lidocaine. Two-thirds of SVT patients were treated successfully with anti-arrhythmic medications without maternal or

fetal complications [18]. DC cardioversion and catheter ablation have been reported to be safe and effective during pregnancy [1, 2]. In patients with significant arrhythmias, prepregnant ablation should be performed, because of the possibility of recurrent arrhythmias during the pregnancy.

When patients with bradyarrhythmias are suspected to worsen during pregnancy, pacemaker (PM) implantation is recommended prior to pregnancy [19]. Regarding catheter ablation or implantable cardioverter defibrillator (ICD) or PM implantation during pregnancy, using echocardiography or 3D mapping system could be used to reduce the radiation exposure time. Patients with implanted pacemaker (fixed rate atrial or ventricular pacing) or ICD before pregnancy are able to tolerate pregnancy well [18].

1.9 Cardiac Failure

Women experiencing cardiac failure after delivery are more common than during pregnancy. For example, small single-center studies in women with repaired tetralogy of Fallot (TOF) have suggested that unfavorable right ventricular remodeling persists after delivery [20, 21]. Volume overload and tachycardia are the triggers of cardiac failure during pregnancy in patients with HD. Decreased systemic vascular resistance can induce low cardiac output with low peripheral perfusion and may lead to deterioration of the mother. Left ventricular end-diastolic pressure can become elevated due to excessive volume overload followed by elevated pulmonary artery hypertension and pulmonary edema. Peripheral edema subsequently appears due to the elevated venous pressure. Cardiac failure can induce maternal arrhythmias and death, if it becomes sufficiently severe. Also, in such cases, the fetus can be aborted or become low birthweight/premature infants. Therefore, women with NYHA III–IV are advised not to become pregnant [22].

1.10 Drug Therapy During Pregnancy

Drugs used for pregnant women must be selected after careful consideration of the risk-benefit balance to the mother and fetus. The adverse effects of drugs on fetus are classified into teratogenic effects and fetal toxicity. While many drugs are excreted substantially into the breast milk of the mother, 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 US FDA is often referred to as important information on the risk of drugs to the fetus or neonate [1]. When drugs contraindicated for pregnant women in the package inserts or drugs not accepted by the National Health Insurance (NHI) are used, 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 in the second and third trimester,

since they may directly affect the kidney of the fetus and neonate, leading to renal failure, abortion, or stillbirth [23, 24]. Furthermore, each of these medications exhibit teratogenicity. Amiodarone is essentially contraindicated for pregnant women since it may cause abnormal thyroid function in the fetus. Bosentan is absolutely contraindicated for pregnant women according to the FDA's recommendation. Warfarin exhibits teratogenicity when administered during the first trimester and increases the risk for bleeding disorders in the fetus and neonate. While heparin does not exhibit fetal toxicity because it does not cross the placenta, 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 is considered to be relatively safe. However, "aspirin is contraindicated for women in the last 12 weeks gestation (regardless of the dose)," especially high-dose aspirin, in the package insert; physicians must fully explain the risks and benefits of aspirin therapy during the second and third trimester of pregnancy to obtain consent from the patient [1].

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 heparin or low-molecular-weight heparin is reasonable for patients undergoing prolonged bed rest. Full anticoagulation can be useful for high-risk patients. While there is no evidence of teratogenicity of the NOACs (novel oral anticoagulants), these medications are not effective for mechanical valves.

1.11 Care Facilities for Pregnancy

Women with HD in whom pregnancy poses a risk must be planned for and monitored carefully for safer pregnancy and childbirth. High-risk pregnancies should be monitored in tertiary care facilities in which a team approach including obstetricians, heart disease specialists (cardiologists, pediatric cardiologists, specialists of congenital heart disease in adults, and cardiovascular surgeons), anesthesiologists, and neonatologists with knowledge and experience in the management of high-risk pregnancy has been established [1, 3]. Every tertiary care facility in which pregnancy and childbirth in women with HD are managed should establish such a specialist team. Hospitals that cannot establish such a team within the institutions should build a system to facilitate consultation with HD specialists in other hospitals.

1.12 Invasive Treatment During Pregnancy

It has been reported that intervention with balloon catheters during pregnancy is effective for patients with pulmonary, aortic, or mitral stenosis [25, 26]. However, these interventions are usually considered to be a kind of emergency rescue. Thus, the indication for intervention is different from those patients who are not pregnant.

The indication for intervention should be manifesting symptoms due to severe cardiac failure which is life threatening to both the mother and fetus. In cases of pulmonary stenosis, indication is symptom plus pressure gradient >50 mmHg between pulmonary artery and right ventricule. In cases with aortic stenosis, indication of intervention is a pressure gradient between aorta and left ventricule of >50 mmHg or aortic orifice size of 0.6 cm^2/m^2. In cases with aortic stenosis, care must be taken not to induce secondary severe aortic regurgitation. In case with mitral stenosis: indication of intervention is symptoms of pulmonary congestion or atrial fibrillation [1].

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

The management of pregnant women who require cardiopulmonary bypass poses problems that are difficult to solve. While the fetus is at greatest risk in the early pregnancy, the mother is at greatest risk later in the pregnancy. Cardiovascular surgery is rarely required during pregnancy, but it can become necessary in some cases [2]. The indication of emergency cardiovascular surgery in women with aortic stenosis during pregnancy should be worsening of valvular regurgitation or the 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 16–20 weeks' gestation or 24–28 weeks' gestation or thereafter, which is safer to the fetus than the other periods. When surgery can wait to 28–30 weeks' gestation or thereafter, surgery after childbirth may become feasible [27, 28]. Cardiovascular surgery with cardiopulmonary bypass during pregnancy is very risky for both the mother and fetus. For the maintenance of low perfusion during bypass, high blood flow and relatively high pressure are inevitable. Fetal mortality has been reported to be 9–30% [29]. On the other hand, mortality of the mother is low compared with the fetus, but the complication rate of the mother remains high. Therefore, it is better to avoid cardiovascular surgery during pregnancy.

1.13 Infective Endocarditis

The guidelines for the prevention and treatment of infective endocarditis [30] recommend that the prevention of infective endocarditis should be considered for most patients with CHD (Table 1.4). 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 cesarean section, etc. Antibiotic treatment of infective endocarditis should be performed in a fashion similar to that for nonpregnant patients according to the susceptibility of causative agents. Preventive administration of antimicrobial agents during delivery is recommended for patients at risk for infective endocarditis [31, 32]. At present, there is no consensus for the preventive administration of antimicrobial agents during delivery. Table 1.5 lists the common measures to prevent infective endocarditis associated with urogenital or gastrointestinal surgeries/procedures [30] (see Chap. 7).

Table 1.4 Patients with heart diseases who should receive preventive antimicrobial treatment throughout pregnancy

Obstetric operations/procedures and delivery
• Patients with a history of infective endocarditis
• Patients with congenital heart disease
– Patients with cyanotic heart disease
– Patients who have undergone repair using artificial patches and devices within the last 6 months
– Patients who have undergone repair and have remaining shunts around the implanted artificial patches and devices
• Patients using artificial valves

Table 1.5 Prevention of infective endocarditis in patients undergoing urogenital or gastrointestinal surgery/procedures

Patients treatment
• Patients with heart disease in whom serious endocarditis may occur
A, Patients who are not allergic to ampicillin/amoxicillin
Administer ampicillin 2.0 g and gentamycin 1.5 mg/kg (maximum dose 120 mg) intramuscularly or intravenously ≤30 min before delivery. Administer intravenous ampicillin 1.0 g or oral amoxicillin 1.0 g, 6 h after delivery
B, Patients who are allergic to ampicillin/amoxicillin
Administer intravenous vancomycin 1.0 g (infuse over 1–2 h) and intramuscular or intravenous gentamycin 1.5 mg/kg (maximum dose 120 mg) to conclude administration ≤30 min before delivery
• Other patients
A, Patients who can take drugs orally
Administer oral amoxicillin 2.0 g (at lower doses for small patients) 1 h before delivery
B, Patients who cannot take drugs orally
Administer intravenous or intramuscular ampicillin 2.0 g ≤30 min before delivery
Patients who are allergic to ampicillin/amoxicillin ampicillin/amoxicillin
Administer intravenous vancomycin 1.0 g (infuse over 1–2 h) to conclude administration ≤30 min before delivery

1.14 Summary

The outcome of pregnancy is favorable in most women with HD provided that functional class and systemic ventricular function are good. Pulmonary artery hypertension presents a serious risk during pregnancy, particularly when the pulmonary pressure exceeds 70% of systemic pressure, irrespective of functional class. Events often occur after delivery [33].

Among the various HDs, CHD represents the most common cause of maternal morbidity. Better assessment and management of this group of patients are likely to make a substantial improvement in outcomes for the mother and fetus [33–35]. There remain a small group of patients with complex CHD or high-risk HD in whom pregnancy is either dangerous or contraindicated owing to the risk to the mother or 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 HD.

Medications should be used only when necessary in any pregnant woman with HD. Certain medications are contraindicated during pregnancy; therefore, those should also be discontinued before pregnancy or early during pregnancy [36]. Although infective endocarditis is a recognized risk for maternal morbidity and mortality, prophylaxis for endocarditis around the time of delivery is recommended for most women with HD. Breast-feeding is feasible in most women with HD. 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.

1.15 Conclusions

In management of women with heart disease and pregnancy, the following items are mandatory:

1. Counseling and risk assessment
2. Preconception medication adjustments, catheter intervention including arrhythmia ablation, or reparative surgery
3. Maternal and fetal monitoring including fetal echocardiography
4. Planning for labor and delivery
5. Cardiac monitoring and follow-up after the postpartum period

References

1. Niwa K, Aomi S, Akagi T, et al Diagnosis and treatment of cardiovascular diseases (2009 Joint Working Groups Report). Guidelines for indication and management of pregnancy and delivery in women with heart disease (JCS 2010, revised). http://www.j-circ.or.jp/guideline/pdf/JCS2010niwa.h.pdf
2. JCS Joint Working Group (2012) Guidelines for indication and management of pregnancy and delivery in women with heart disease (JCS 2010) digest version. Circ J 76:240–260

3. Gelson E, Ogueh O, Johnson M (2006) Cardiac changes in normal pregnancy. In: Steer PJ, Gatzoulis MA, Baker P (eds) Heart disease and pregnancy. RCOG Press, London, pp 29–44
4. Mabie WC, DiSessa TG, Crocker LG et al (1994) A longitudinal study of cardiac output in normal human pregnancy. Am J Obstet Gynecol 170:849–856
5. Poppas A, Shroff SG, Korcarz CE et al (1997) Serial assessment of the cardiovascular system in normal pregnancy. Circulation 95:2407–2415
6. Niwa K, Perloff JK, Bhuta SM et al (2001) Structural abnormalities of great arterial walls in congenital heart disease: light and electron microscopic analyses. Circulation 103:393–400
7. Katsuragi S, Ueda K, Yamanaka K et al (2011) Pregnancy-associated aortic dilatation or dissection in Japanese women with Marfan syndrome. Circ J 75:2545–2551
8. Niwa K, Tateno S, Akagi T et al (2007) Arrhythmia and reduced heart rate variability during pregnancy in women with congenital heart disease and previous reparative surgery. Int J Cardiol 122:143–148
9. Ohuchi H, Tanabe Y, Kamiya C et al (2013) Cardiopulmonary variables during exercise predict pregnancy outcome in women with congenital heart disease. Circ J 77:470–476
10. Kamiya C, Nakatani S, Hashimoto S et al (2008) Role of echocardiography in assessing pregnant women with and without heart disease. J Echocardiogr 6:29–38
11. Colman JM, Silversides CK, Sermer M et al (2006) Cardiac monitoring during pregnancy. In: Steer PJ, Gatzoulis MA, Baker P (eds) Heart disease and pregnancy. RCOG Press, London, pp 67–77
12. DeWilde JP, Rivers AW, Price DL (2005) A review of the current use of magnetic resonance imaging in pregnancy and safety implications for fetus. Prog Biophys Mol Biol 87:335–353
13. Silka M, Hardy B, Menashe V et al (1998) A population-based prospective evaluation of risk of sudden cardiac death after operation for common congenital heart defects. J Am Coll Cardiol 32:245–251
14. Gatzoulis MA, Balaji S, Webber SA et al (2000) Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicenter study. Lancet 356:975–981
15. Shotan A, Ostrzega E, Mehra A et al (1997) Incidence of arrhythmias in normal pregnancy and relation to palpitations, dizziness, and syncope. Am J Caridiol 79:1061–1064
16. Joglar JA, Page RL (2001) Antiarrhythmic drugs in pregnancy. Curr Opin Cardiol 16:40–45
17. Brodsky M, Doria R, Allen B et al (1992) New-onset ventricular tachycardia during pregnancy. Am Heart J 123:933–941
18. Tateno S, Niwa K, Nakazawa M et al (2003) Arrhythmia and conduction disturbances in patients with congenital heart disease during pregnancy – multicenter study. Circ J 67: 992–997
19. Dalvi BV, Chaudhuri A, Kulkarni HL et al (1992) Therapeutic guidelines for congenital heart block presenting in pregnancy. Obstet Gynecol 79:802–804
20. Egidy AG, Cassater D, Landzberg M et al (2013) The effects of pregnancy on right ventricular remodeling in women with repaired tetralogy of Fallot. Int J Cardiol 168:1847–1852
21. Kamiya CA, Iwamiya T, Neki R et al (2012) Outcome of pregnancy and effects on the right heart in women with repaired tetralogy of Fallot. Circ J 76:957–963
22. Siu SC, Sermer M, Harrison DA et al (1997) Risk and predictors for pregnancy-related complications in woman with heart disease. Circulation 96:2789–2794
23. Buttar HS (1997) An overview of the influence of ACE inhibitors on fetal-placental circulation and perinatal development. Mol Cell Biochem 176:61–71
24. Cooper WO, Hernandez-Diaz S, Arbogast PG et al (2006) Major congenital malformations after first-trimester exposure to ACE inhibitors. N Engl J Med 354:2443–2451
25. Presbitero P, Prever SB, Brusca A (1996) Interventional cardiology in pregnancy. Eur Heart J 17:182–188
26. Wloch A, Respondek-Liberska M, Sysa A et al (2004) Significant aortic and pulmonary valve stenosis in the prenatal period: diagnosis, treatment and outcome: a two-centre study. Acta Cardiol 59:242–243
27. Parry AJ, Westaby S (1996) Cardiopulmonary bypass during pregnancy. Ann Thorac Surg 61:1865–1869
28. Colman JM, Sermer M, Seaward PG et al (2000) Congenital heart disease in pregnancy. Cardiol Rev 8:166–173

29. Child J, Perloff JK, Koos B (2009) Management of pregnancy and contraception in congenital heart disease. In: Perloff JK, Child JS, Aboulhosn J (eds) Congenital heart disease in adults, 3rd edn. Saunders/Elsevier, Philadelphia, pp 194–220
30. Guidelines for the Diagnosis and Treatment of Cardiovascular Diseases (2007 Joint Working Groups Report) Guidelines for the Prevention and Treatment of Infective Endocarditis (JCS 2008). http://www.j-circ.or.jp/guideline/pdf/JCS2008_miyatake_h.pdf
31. Stuart G (2006) Maternal endocarditis. In: Steer PJ, Gatzoulis MA, Baker P (eds) Heart disease and pregnancy. RCOG Press, London, pp 267–282
32. Child JS, Pegues DA, Perloff JK (2009) Infective endocarditis and congenital heart disease. In: Perloff JK, Child JS, Aboulhosn J (eds) Congenital heart disease in adults, 3rd edn. Saunders/Elsevier, Philadelphia, pp 168–193
33. Siu SC, Sermer M, Colman JM et al (2001) Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation 104:515–521
34. Khairy P, Ouyang DW, Fernandes SM et al (2006) Pregnancy outcomes in women with congenital heart disease. Circulation 113:517–524
35. Siu SC, Colman JM, Sorensen S et al (2002) Adverse neonatal and cardiac outcomes are more common in pregnant women with cardiac disease. Circulation 105:2179–2184
36. Briggs GG, Freeman RK, Yaffe SJ (eds) (2008) Drugs in pregnancy and lactation, 8th edn. Lippincott Williams & Wilkins, Philadelphia

Intrapartum Management

2

Chizuko Aoki-Kamiya and Jun Yoshimatsu

Abstract

Uterine blood flow increases progressively throughout pregnancy and reaches about 500 ml/min at term. Thus, each uterine contraction causes increased venous return. Right after delivery and placenta expulsion, uterine involution and termination of placental circulation cause an autotransfusion of approximately 300–500 mL of blood. Therefore, intrapartum is one of the peak times when heart failure occurs in women with cardiovascular disease.

Timing of delivery and mode of delivery should be decided in individual cases. Vaginal delivery is preferred, even among women with cardiovascular disease, and Cesarean delivery is reserved for obstetric indications. However, there are several high-risk conditions in which Cesarean section is recommended, such as Marfan syndrome with significantly dilated aorta. The use of regional anesthesia in labor and assisted vaginal delivery can reduce intrapartum hemodynamic changes. High-risk labors require specific expertise and collaborative management by skilled obstetricians, cardiologists, anesthesiologists, and neonatologist in experienced maternal–fetal medicine units.

Keywords

Labor · Anesthesia · Vaginal delivery · Cesarean section · Heart failure

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2.1 Intrapartum Physiological Changes

Blood volume increases further during labor with each uterine contraction, which squeezes uteroplacental blood flow into the central circulation. When regular uterine contractions start, elevated cardiac output (CO), pulmonary artery wedge pressure, and central venous pressure are observed. CO increased by 25–30% in active phase of labor and by 50% in the second stage of labor compared with the value of pre-labor (Table 2.1) [1]. Right after delivery and placenta expulsion, uterine involution and termination of placental circulation cause an autotransfusion of approximately 300–500 mL of blood. Increased venous return by uterine contraction leads to concomitant increase in stroke volume. Pain leads to increased sympathetic nervous activity and endogenous catecholamine which cause elevated blood pressure and heart rate [2]. Increased autonomic activity may be an aggravating factor for arrhythmic events. Epidural anesthesia helps to decrease such changes [3].

Maternal position greatly affects the amount of cardiac output because the gravid uterus causes femoral vein and inferior vena caval obstruction in the supine position. A lateral decubitus position is preferred to attenuate the hemodynamic impact of uterine contractions in some cases.

2.2 Timing of Delivery

Spontaneous onset of labor is the initial choice for women with normal cardiac function and no complications. However, induced labor by oxytocin is also preferable in an individual case and an individual hospital. Preterm delivery should be

Table 2.1 Progression of labor and changes of cardiac output [1]

	First stage of labor		Second stage of labor	Third stage of labor
	Latent phase	Active phase		
Onset	Painful regular contractions	Cervical dilatation of 3 cm and 5 cm	Complete cervical dilatation	Fetal delivery
End	Cervical dilatation of 3 cm and 5 cm	Complete cervical dilatation	Fetal delivery	Placental delivery
Uterine contractions	20–30 s every 10 min or less	30–40 s every 5 min or less	40–60 s every 3 min or less	
Duration				
Nulliparas	12–14 h		1–2 h	15–30 min
Multiparas	6–8 h		0.5–1 h	10–20 min
Cardiac output at contractions[a]	×1.1	×1.3	×1.5	
Stroke volume at contractions[a]	×1.1	×1.2	×1.3	
Heart rate at contractions[a]	×1.0	×1.1	×1.2	

s seconds, *min* minutes, h: hours

[a]The values of pre-labor are prescribed as 1

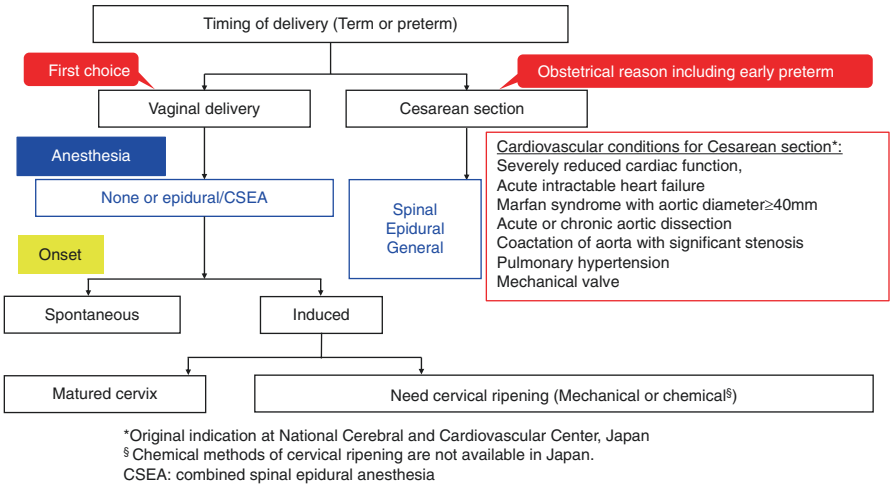

Fig. 2.1 Flowchart of decision-making about timing and mode of delivery

considered when significant cardiovascular and/or obstetrical complications occur in a woman with heart disease. The precise indication for preterm delivery due to cardiovascular events is not clear, because of the lack of evidence. The relative risks of maternal mortality/morbidity and premature neonate are weighed, and then the timing of delivery is decided. Figure 2.1 shows a flowchart of decision-making about timing and mode of delivery.

2.3 Mode of Delivery

Vaginal delivery is preferred among women with cardiovascular disease, and, in general, Cesarean delivery is reserved for obstetric indications. However, there are several high-risk conditions in which Cesarean section is recommended: severely reduced cardiac function, Marfan syndrome with significantly dilated aorta, coarctation of the aorta with significant stenosis, mechanical valves, uncontrolled arrhythmia, patients with cyanosis or pulmonary hypertension in the Japanese guideline [4] and the patient on oral anticoagulants in preterm labor, patients with Marfan syndrome and an aortic diameter >45 mm, and patients with acute or chronic aortic dissection or those in acute intractable heart failure in the European guideline [5]. Cesarean delivery may be also considered in Marfan patients with an aortic diameter of 40–45 mm [5]. These indications should be tailor-made at each hospital. The indications of Cesarean section for cardiovascular conditions at National Cerebral and Cardiovascular Center, Japan are shown in Fig. 2.1. Elective Cesarean section allows the maternal hemodynamics to be kept more stable. Although the cardiac output, during and right after vaginal delivery, increases more than 1.5 times compared with values of pre-delivery [2], the cardiac output during Cesarean section was reported +37% with epidural anesthesia and +28% with general anesthesia [6]. Moreover, induction of labor with immature cervix often fails or takes a long time. Table 2.2

Table 2.2 Pros and cons of vaginal delivery and Cesarean section for maternal conditions

	Vaginal delivery	Cesarean section
Anesthetic agent	None–small	Large
Approximate loss of blood volume (singleton)	400–500 ml	800–900 ml
Duration between fetal and placental delivery	10–30 minutes	Within 5 minutes
Bed rest after delivery	Short (-2 hours)	Long (6–24 hours)
Risk of thromboembolism	Low	High
Setting of delivery date and hour	Difficult (especially with immature cervix)	Possible
Valsalva maneuver	+	–
Increased cardiac output during labor	More	Less

shows the pros and cons of vaginal delivery and Cesarean section from a perspective view of maternal conditions. The delivery mode should be chosen in an individual case and an individual hospital, as well as timing of delivery. Once an individualized delivery plan is decided, the plan should be informed and shared among a team of doctors and nurses. High-risk delivery should be managed by the specialized multidisciplinary team at tertiary centers.

Preventive administration of antimicrobial agents during delivery is recommended for patients with a high risk for infective endocarditis [4] (see Chap. 7).

2.3.1 Management of Vaginal Delivery

Table 2.1 shows the progression of vaginal delivery. The use of regional anesthesia and assisted vaginal delivery can reduce intrapartum hemodynamic changes. Persistent epidural anesthesia and combined spinal–epidural anesthesia are widely used as the regional anesthesia for painless labor. Although oxygen consumption and minute ventilation increase dramatically during labor, due primarily to pain associated with uterine contractions, regional anesthesia decreased the work of breathing and the oxygen consumption of the parturient in both the first and second stages of labor [7].

Cardiovascular indications of regional anesthesia are described in several guidelines. Tachyarrhythmia, mild to moderate stenotic lesions, and cardiomyopathy and Marfan syndrome without significant aortic dilatation are good indications for painless labor in the Japanese guideline [4]. Table 2.3 shows the indications of epidural anesthesia at National Cerebral and Cardiovascular Center, Japan. However, regional anesthesia can cause systemic hypotension and must be very carefully used in patients with severe obstructive lesions, such as aortic stenosis and hypertrophic obstructive cardiomyopathy.

To avoid the effects of the Valsalva maneuver and to shorten the duration of the second stage of labor, the assisted delivery by low forceps or vacuum extraction is also recommended for women with significant cardiovascular disease, such as women with Fontan circulation or Marfan syndrome with dilated aorta.

Table 2.3 The cardiovascular indications for painless labor at National Cerebral and Cardiovascular Center in Japan

Absolute indications
Marfan syndrome with aortic dilatation
Bicuspid aortic valve with significant aortic dilatation (>45 mm)
Congenital heart disease with significant aortic dilatation (>50 mm)
Reduced left ventricular ejection fraction (<40%)
Unrepaired cyanotic congenital heart disease and Fontan circulation
Unrepaired or post balloon angioplasty for coarctation of the aorta
Active heart failure without any indication of Cesarean section
Relative indications
Tachyarrhythmia
Ischemic heart disease
Aortopathy without absolute indications for painless labor
Moderate to severe valve lesions
Unrepaired acyanotic congenital heart disease
Cardiomyopathy

During the third stage of labor, uterine contraction is very important to avoid atonic bleeding. A low-dose oxytocin infusion after placental delivery is used more safely than a bolus shot of oxytocin, which may cause systemic hypotension. Methylergonovine should not be used for women with heart disease because of the risk of vasospasm and hypertension.

2.3.2 Management of Cesarean Delivery

Anesthesia in Cesarean delivery is well described in a later chapter (see Chap. 3). Because Cesarean delivery has more risk of venous thrombosis, prophylaxis such as low-molecular-weight heparin and elastic support stockings is recommended.

2.4 Maternal Monitoring

Hemodynamic parameters, such as systemic arterial blood pressure and maternal heart rate, should be monitored during delivery. Lumbar epidural anesthesia and bolus oxytocin may cause hypotension. Pulse oximetry and continuous electrocardiogram (ECG) monitoring are utilized as required. A Swan–Ganz catheter is rarely indicated, due to the risk of arrhythmia provocation, bleeding and thromboembolism (Severe pulmonary hypertension is an exception). Simple echocardiography is helpful to determine hemodynamic conditions, even in parturient woman.

References

1. Robson SC, Dunlop W, Boys RJ, Hunter S (1987) Cardiac output during labour. Bri Med J 295:1169–1172
2. Ouzounian JG, Elkayam U (2012) Physiologic changes during normal pregnancy and delivery. Cardiol Clin 30:317–329
3. Tanaka H, Kamiya C, Katsuragi S et al (2018) Effect of epidural anesthesia in labor; pregnancy with cardiovascular disease. Taiwan J Obstet Gynecol 57:190–193
4. JCS Joint Working Group (2012) Guidelines for indication and management of pregnancy and delivery in women with heart disease. Circ J 76:240–260
5. ESC Guidelines on the management of cardiovascular diseases during pregnancy. The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC) (2011). https://doi.org/10.1093/eurheartj/ehr218.
6. James CF, Banner T, Caton D (1989) Cardiac output in women undergoing cesarean section with epidural or general anesthesia. Am J Obstet Gynecol 160:1178–1184
7. Hagerdal M, Morgan CW, Sumner AE, Gutsche BB (1983) Minute ventilation and oxygen consumption during labor with epidural analgesia. Anesthesiology 59:425–427

Obstetric Anesthesia

3

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Abstract

Despite advances in anesthetic and obstetric care, cardiovascular disease in pregnancy continues to cause significant rates of morbidity and mortality in obstetric surgery. As a growing population of adults with congenital heart disease reaches childbearing age, the incidence of cardiovascular disease in pregnancy has been dramatically increasing. As a result, anesthesiologists are also increasingly faced with managing cesarean sections in patients with pre-existing cardiovascular disease. Cesarean delivery is inherently one of the most challenging surgeries for such patients. This chapter focuses on perioperative anesthetic management for cesarean section in this population. The major anesthetic goal is to achieve a multidisciplinary-based optimization of maternal hemodynamics to improve outcomes for the two patients, mother and baby. There is unfortunately no definitive evidence to guide anesthesiologists on how to best manage cesarean patients with cardiovascular disease. Consequently, the author's recommended approach described herein is primarily based on physiological principles, as well as on personal experience. Therefore, a thorough understanding of the pathophysiology, available options for anesthesia, and potential complications is crucial if today's anesthesiologist is to optimize hemodynamics in mothers with cardiovascular disease who are undergoing cesarean section.

Keywords

Anesthesia · Cesarean section · Cardiovascular disease

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Pregnant patients with cardiovascular disease (CVD) pose a significant challenge to anesthesiologists, as pregnancy itself imposes profound stress on an already compromised cardiovascular system. Heart disease is currently one of the leading causes of maternal mortality. Cardiovascular diseases affect up to 4% of all pregnancies in the Western world [1, 2]. Consequently, patients with CVD are increasingly common in the obstetric perioperative setting. However, high-quality scientific evidence on the types of anesthetic management best suited to this population is currently lacking. Thus, there is no consensus regarding ideal anesthetic management for labor and delivery in CVD patients [1, 2]. As it stands now, obstetric anesthesia in CVD is performed based on the empirical evidence and experience of expert anesthesiologists. The major concern about CVD in pregnancy is the development of heart failure as the pregnancy evolves toward delivery. The early postpartum period, moreover, represents a high-risk time for sudden death [1, 2]. To prevent maternal heart failure and sudden death, the primary anesthetic goal remains the optimization of maternal hemodynamics throughout the perioperative period.

Cesarean section is the most common surgical obstetric procedure for women with CVD. Most patients with CVD tolerate pregnancy, labor, and vaginal delivery well, although the selection criteria of delivery mode for borderline cases are still debatable [1, 2]. The patient requiring cesarean section is considered to be at significantly high risk. Therefore, this chapter focuses on anesthetic management for cesarean delivery in patients with CVD.

3.1 General Considerations

3.1.1 Maternal Risk Stratification for Cesarean Section in Cardiovascular Disease

Several classification forms, such as the CARPREG risk score or the modified WHO risk classification, are available for assessing the risk of maternal cardiovascular complications in CVD patients [1, 3, 4]. There is, however, no reliable specific risk stratification for cesarean section. In our institute, maternal risk estimation for cesarean delivery is performed as described herein and as shown in Table 3.1. Pregnant women with CVD necessitating cesarean section fall into three categories: low risk (e.g., anatomically repaired congenital heart disease without severe ventricular dysfunction or moderate to severe pulmonary hypertension (PH), aortic dilatation, maternal cardiac transplant); intermediate risk (e.g., PH of any origin with a mean pulmonary artery pressure (PAP) of less than 50 mmHg or equal, functional repaired congenital heart disease, uncorrected cyanotic heart disease without PH, moderate to severe systemic outflow obstruction, or emergency delivery due to obstetric events); and high risk (Eisenmenger syndrome, PH of any origin with a mean PAP of more than 50 mmHg, any disease with malignant arrhythmias, or emergency delivery due to maternal cardiovascular events). Pregnant patients with intermediate- and high-risk CVD should be managed in specialized institutes with expertise and experience in anesthesiology.

Table 3.1 Maternal risk stratification for cesarean section in cardiovascular disease

Low risk
Anatomical repaired CHD without severe ventricular dysfunction or moderate to severe PH
Uncorrected simple shunt lesion with no or mild PH
Mild systemic outflow obstructive lesion
Mild to moderate valve regurgitation
Mild to moderate ventricular impairment
Repaired valve disease
Ischemic heart disease
Maternal cardiac transplant
Aortic dilatation
Moyamoya disease
Presence of pacemaker or defibrillator
Isolated ectopic beats or prior history of arrhythmias
Intermediate risk
PH of any origin with mean PAP of less than 50 mmHg or equal
Functional repaired CHD
Uncorrected simple shunt lesion with moderate PH
Uncorrected cyanotic heart disease without PH
Moderate to severe systemic outflow obstruction
Severe valve regurgitation
Severe ventricular dysfunction
Emergency delivery due to obstetric events
High risk
Eisenmenger syndrome
PH of any origin with mean PAP of more than 50 mmHg
Any disease with malignant arrhythmias
Emergency delivery due to maternal cardiovascular events

CHD congenital heart disease, *PAP* pulmonary artery pressure, *PH* pulmonary hypertension

3.1.2 Physiological Changes in Pregnancy (See Chaps.1 and 2)

3.1.2.1 Hemodynamic Changes

Pregnancy itself induces profound changes in the circulatory system in order to meet the increased metabolic demands of the mother and fetus [1, 2, 5]. Hemodynamic alterations in the maternal circulation start as early as in the first trimester, plateauing at the third trimester, and continue for 2 weeks to 6 months postpartum or longer. Blood volume, heart rate, cardiac output, and a decrease in systemic and pulmonary vascular resistances (SVR and PVR, respectively) are all increased. Blood volume reaches a plateau at around 32 weeks of gestation. The increased blood volume and subsequent cardiac remodeling lead to significant increases in left ventricular wall thickness and mass, as well as in end-diastolic dimension. Importantly, blood volume expansion is widely known to vary significantly from patient to patient: some show a 200% increase. Stroke volume declines in the third trimester due to aortocaval compression by the gravid uterus. Reports on cerebral

blood flow are conflicting [6–9]. The glomerular filtration rate increases early in the first trimester and remains elevated throughout pregnancy. The serum creatinine level is about 0.5 mg/dl in pregnancy. Normal creatinine levels in nonpregnant women may actually point to kidney injury during pregnancy [10].

It is in the delivery and early postpartum periods that hemodynamic changes are most pronounced [1–3]. Pain, anxiety, uterine contractions, and aortocaval decompression can further, and abruptly, increase the blood volume, heart rate, and cardiac output to 80% above baseline levels. Uterine contractions augment the cardiac preload by up to 300–500 ml. The expulsion or removal of the placenta accelerates elevations in both the cardiac preload and afterload immediately postpartum. Pregnancy-related hemodynamics usually resolve within 2 weeks after delivery, although some patients may take up to 6 months or longer.

3.1.2.2 Respiratory Changes

Oxygen consumption is increased, thereby requiring augmented alveolar ventilation [11]. Functional residual capacity is decreased owing to uterus enlargement [1]. Increased oxygen consumption and decreased functional residual capacity can cause oxygen desaturation during endotracheal intubation. Despite reduced levels of arterial carbon dioxide tension ($PaCO_2$ 28–33 mmHg) following hyperventilation, blood pH typically remains normal due to renal compensation during pregnancy (serum bicarbonate 18–21 mEq/l) [11]. Peak oxygen uptake, a parametric measure of cardiopulmonary capacity, is maintained. The lung compliance does not change during pregnancy, whereas chest wall and total respiratory compliance are lower at term. Forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) remain unchanged within the normal range of predicted values (FEV1% and FVC%, respectively) [12]. FEV1 and FVC values are same in both singleton and twin pregnancies [13]. Pregnant women are vulnerable to hydrostatic pulmonary edema due to dilutional reductions in plasma colloid oncotic pressure [11]. Airway anatomical alterations occur during pregnancy and include mucosal edema of the respiratory tract and capillary engorgement of nasal and oropharyngeal mucosa [14]. Oral intubation using a smaller endotracheal tube is recommended for general anesthesia.

3.1.2.3 Hemostatic Changes

Cesarean section is usually associated with a blood loss of 500–800 ml. Pregnancy presents a hypercoagulable state characterized by plasma value elevation in all clotting factors except for factors XI and XIII. Fibrinogen and prothrombin increase, while fibrinolysis is diminished. Platelet count is often decreased [15]. Benign gestational thrombocytopenia occurs in about 8% of pregnant women, usually presents mild thrombocytopenia with normal platelet function, and spontaneously resolves postpartum. Pregnancy predisposes patients to venous stasis in their lower extremities, thereby increasing the risk of thromboembolism. Unfractionated heparin or low molecular weight heparin, commonly used as an anticoagulant in pregnancy, does not cross the placenta into the fetal circulation.

3.1.2.4 Fetal Oxygenation

Fetal oxygenation, as assessed by the partial pressure of oxygen (PO_2) in umbilical venous blood, is far lower than maternal arterial PO_2 (fetal PO_2 25–30 mmHg) [6,

16]. Blood flow and oxygen content in the utero-placenta determine oxygen delivery to the fetus via the umbilical vein. Uterine blood flow measures about 500–700 ml/min at term. Uteroplacental perfusion is not autoregulated due to the already maximally dilated vasculature [16]. Thus, fetal oxygen delivery greatly depends on maternal systemic aortic blood pressure and cardiac output. Mild to moderate hypo- and hypercapnia (end-tidal CO_2 < 23 mmHg and 40–60 mmHg) in late gestational women have no significant impact on fetal heart rate variability or on the number of fetal heart rate accelerations. This indicates that mild-to-moderate alterations in maternal $PaCO_2$ may exert little effect on fetal oxygenation. Nonetheless, maternal hypercapnia may increase fetal oxygen consumption since vigorous respiratory movements are often induced in the fetus [17]. In animal studies, maternal respiratory alkalosis (moderate-to-severe hypocapnia) was associated with a decrease in uteroplacental flow and, thus, fetal oxygenation [16, 18]. The effects of moderate-to-severe hypercapnia on the fetus remain unclear. One clinically controlled study demonstrated that short-term moderate hypercapnia (mean $PaCO_2$ 57.6 mmHg) is associated with higher Apgar scores compared to mild hypocapnia (mean $PaCO_2$ 26.4 mmHg) or to the normocapnia expected during pregnancy (mean $PaCO_2$ 30.1 mmHg) [19]. However, hypercapnia may theoretically result in fetal respiratory acidosis, as was shown in an animal study in which bicarbonate ions slowly crossed the placenta [18]. Ovine hypercapnia has been shown to cause uterine artery vasoconstriction and reduced uterine blood flow. Acidosisinduced myocardial depression in the fetus may cause fetal organ hypoxia and further severe acidosis. Utero-placental oxygen content seems to have significantly less effect on fetal oxygenation compared to blood flow. In a clinical interventional study of acute maternal hypoxemia (maternal arterial oxygen saturation < 85%), there were no clear adverse impacts on fetal monitoring parameters [20]. Fetal hemoglobin has a greater affinity for oxygen than maternal hemoglobin, enhancing the placental uptake of oxygen [16]. The fetus may therefore tolerate acute maternal hypoxemia, although maternal hypoxemia in one animal model study not only caused decreased placental oxygen content, but also uteroplacental vasoconstriction, resulting in fetal hypoxia and acidosis [18].

3.1.3 Multidisciplinary Communications

Close collaboration and active communication among anesthesiologists, obstetricians, neonatologists, cardiologists, and cardiac surgeons are needed for optimal anesthetic care of cesarean section patients with CVD. Anesthesiologists should also assume a leadership role in the operating room to achieve 100% team performance. Importantly, anesthesia consultation should occur in advance of labor and delivery, even in cases of planned vaginal delivery. The possibility of an early cesarean section should always be kept in mind, given that hemodynamic conditions can unexpectedly deteriorate, and should be undertaken before circumstances worsen to a dangerous degree. Potential maternal-fetal triage scenarios in cesarean section patients should be discussed in advance. The sooner anesthesiologists start planning an obstetric anesthesia, the more reliable anesthesia they can perform. A cardiac intensive care unit would be favorable for postoperative care. A multidisciplinary team approach is obviously essential in the management of patients with CVD for cesarean delivery.

3.2 Neuraxial Versus General Anesthesia for Cesarean Section

Preoperative treatment to stabilize the hemodynamics of a patient is critical. Once a patient's hemodynamics has stabilized, either neuraxial or general anesthesia is acceptable. The advantages and disadvantages of neuraxial and general anesthesia are summarized in Table 3.2. Typical anesthetic options for patients undergoing

Table 3.2 Neuraxial versus general anesthesia for cesarean section in cardiovascular patients

	Neuraxial	General
Advantages	Avoids positive-pressure ventilation Reduces incidence of respiratory depression and failure Avoids potentially hemodynamic instability associated with endotracheal intubation Avoids manipulation of difficult airways Allows the patient to be transferred from the operating room immediately after surgery Provides excellent long-lasting postoperative analgesia	Can be performed in all patients Can intubate difficult airways under controlled conditions before surgery Avoids the risk of intraoperative conversion to general anesthesia May be more favorable to electrical cardioversion Allows transesophageal echocardiography monitoring May be superior to neuraxial anesthesia in terms of cardiopulmonary resuscitation May allow an extracorporeal membrane oxygenation (ECMO) system to be instituted without risk of spinal/epidural hematoma
Disadvantages	Cannot be performed in all patients because of the existence of contraindications (e.g., maternal refusal or coagulopathy) and anatomical problems May need the emergent conversion to general anesthesia with endotracheal intubation during surgery Carries risks of acute hypotension and bradycardia induced by sympathectomy May develop heart failure and/or pulmonary edema if the abrupt resolution of the sympathectomy coincides with fluid volume expansion postpartum May take longer to produce adequate anesthesia than dose general anesthesia May worsen maternal emotional stress while awake Poses a theoretic concern about failed anesthesia Needs adequate positioning for a block May not allow patients with orthopnea, due to severe cardiac disease, to tolerate the supine position while awake Has a risk of local anesthetic toxicity	May cause hemodynamic instability during induction and emergence Needs positive-pressure ventilation, potentially leading to abruptly decreased venous return and cardiac output Needs tracheal extubation Needs to continue sedation if ventilator support is required after surgery Adversely affects the cardiovascular system because of systemic administration of anesthetic drugs May increase the risk of aspiration pneumonitis Poses a theoretical concern about failed intubation May need systemic opioid analgesia after surgery

cesarean section include spinal anesthesia, epidural anesthesia, general anesthesia, and combinations of them. It is up to the anesthesiologist to judiciously decide whether the benefits outweigh the risks in each specific patient.

3.2.1 Elective Cesarean Section

Neuraxial anesthesia (i.e., spinal, epidural, or combined spinal-epidural (CSE) anesthesia) is generally preferable in pregnant women with CVD [1, 2]. There is at least some evidence to suggest that general anesthesia may be associated with an increased risk of surgical death in this population [21–23]. In fact, general anesthesia carries potentially higher risks, such as hemodynamic instability during induction and emergence, compared to neuraxial anesthesia. However, general anesthesia is occasionally chosen, particularly in patients with a high likelihood of rapid hemodynamic deterioration, by expert anesthesiologists who are well versed in the special hemodynamic aspects of complex congenital heart disease, chronic thromboembolic pulmonary hypertension, and end-stage heart failure requiring ventricular assist device implantation. There are five reasons for this. First, the highest priority of the anesthetic strategy is avoiding the need for intraoperative conversion of neuraxial to general anesthesia due to obstetric or anesthetic complications because emergent induction of general anesthesia under neuraxial blockade may cause catastrophic adverse events. Second, general anesthesia is more favorable to electrical cardioversion for the treatment of newly developed arrhythmias including supraventricular tachycardia, atrial fibrillation, or flutter. Third, a transesophageal echocardiography (TEE) monitor can be easily used to determine the cause of any unexplained cardiovascular events. Fourth, although there is as yet no conclusive evidence, experienced anesthesiologists believe that general anesthesia with endotracheal intubation is superior to neuraxial anesthesia in terms of cardiopulmonary resuscitation in pregnant women with CVD. Finally, systemic heparin can be used without risks of spinal/epidural hematoma in those cases requiring the use of an extracorporeal membrane oxygenation (ECMO) system. There is a systematic review demonstrating similar operative mortality rates for cesarean delivery in Eisenmenger patients, who are regarded as the highest-risk cases, using either neuraxial or general anesthesia (Table 3.1) [24].

3.2.2 Emergency Cesarean Section

Some pregnant women with CVD may require an emergency cesarean section [25], which rank among the most challenging scenarios. Regardless of CVD severity, all emergency cases should be considered intermediate or high risk (Table 3.1).

General anesthesia must be performed in all true emergencies with particular caution regarding failed intubation and aspiration. Induction of general anesthesia in a high-risk group (Table 3.1) may take longer than usual. In case in which a difficult airway is anticipated, additional induction time may be required. TEE, which must be inserted gently, could replace a central venous pressure (CVP) catheter to monitor preload and correct heart performance.

Neuraxial anesthesia is acceptable in most emergent CVD cases lacking absolute contraindications, such as maternal refusal or severe coagulopathy. Single-shot spinal anesthesia is not recommended, at least in high-risk populations (Table 3.1) [26–29]. Although single-shot spinal anesthesia may indeed be quicker, it may cause profound hemodynamic compromise, thereby further worsening uteroplacental perfusion and newborn outcomes. Abrupt resolution of spinal-induced sympathectomy may increase the risk of circulatory overload along with delivery-related autotransfusion, particularly in high-risk populations (Table 3.2).

3.3 Contingency Plans

Anesthesiologists should always prepare contingency treatment plans for obstetrical and cardiopulmonary adverse events. The possible need for a perimortem cesarean section should always be kept in mind. It should be specifically discussed beforehand whether ECMO standby is needed. Although the efficacy of extracorporeal cardiopulmonary resuscitation remains unclear in pregnant women with CVD, ECMO support for acute respiratory failure in pregnancy has recently been shown to be effective and relatively safe, with survival rates of 77.8% (33 of 45) for mothers and 65% (28 of 43) for fetuses [30]. A feasibility assessment of vascular access points or the advance insertion of small introducer gates into the femoral, axillary, or cervical site facilitates proper percutaneous institution of ECMO.

3.4 Neuraxial Anesthesia

Neuraxial anesthesia is a reasonable anesthetic option for planned cesarean section in CVD. A very slowly titrated epidural anesthesia can achieve at least a thoracic-6 (T6) dermatomal sensory level of analgesia. Epidural anesthesia is known to confer a lower risk of clinically significant hypotension compared to spinal anesthesia [31]. For CVD parturients, epidural anesthesia offers better hemodynamic stability. In the case of a pre-existing epidural catheter for labor analgesia, an epidural top-up (extension of a labor epidural) may be the best approach for an emergent cesarean section without posing any threat either to the mother or the fetus. Postpartum analgesia can be provided through continuous epidural infusion of local anesthetic with an opioid to suppress pain-related stress, thereby reducing the need for systemic opioid treatment. While patient-controlled epidural analgesia remains the standard technique for postsurgical analgesia, whether this technique is safe in the CVD patients following cesarean section has yet to be conclusively determined.

3.4.1 A Suggested Technique for Epidural Anesthesia

In our institution, most low- or intermediate-risk parturients (Table 3.1) are considered suitable for epidural anesthesia alone for cesarean section. Mepivacaine is our

preferred local anesthetic because of its lower neurotoxicity compared to that of lidocaine [32]. Incremental doses of 2% mepivacaine (2–3 ml every 3–5 min) are administered. In addition, epidural fentanyl 100–200 mcg (2–4 ml) is applied following the initial or second injection of mepivacaine. To obtain a T4 surgical level, the usual range is 8–14 ml of mepivacaine. It is essential to regard each subsequent dose as a test dose. Additional 3 ml epidural doses and/or commencement of continuous infusion of 2% mepivacaine (3–6 ml/h) may be needed beyond 60 min, beginning from the last dose, in cases of prolonged surgery. The use of epinephrine as an additive to the epidural local anesthetic should be avoided, since even a small intravenous dose may cause significant hemodynamic embarrassment in CVD patients.

A 5-lead electrocardiogram monitor and external defibrillator pads are usually kept on hand in addition to routine monitors. For some low-risk and most intermediate-risk patients (Table 3.1), an intra-arterial catheter is placed prior to performing the epidural. In most intermediate-risk patients, a central venous line is frequently inserted with extreme care to prevent an air embolism in order to optimally control hemodynamics, especially in the early postpartum period. The patient is not placed in the Trendelenburg (head-down) position for central line placement. As all invasive procedures, including epidural needle insertions, are performed in awake patients, caution must be exercised to prevent potentially morbid cardiac events stemming from pain, anxiety, or stress.

Phenylephrine, a pure alpha-1 adrenergic agonist, is often prophylactically iv infused prior to mepivacaine injection at 0.5–1.0 mg/h. Subsequently, additional boluses may be needed (0.05–0.1 mg) to maintain the target blood pressure (the usual maximum dosage is equal to or less than 2.5 mg/h). Patients with PH, systemic outflow tract obstructions, or congenital heart disease with right-to-left shunts do not tolerate low SVR well. Restricted fluid management can reduce the risk of cardiopulmonary complications in most CVD parturients receiving epidural anesthesia alone. Our epidural technique allows us to optimally maintain both cardiac preload and afterload.

3.4.2 Alternative Neuraxial Techniques

Low-dose CSE is suitable for cesarean delivery in CVD patients [33, 34]. This low-dose combination technique involves a small amount of intrathecal bupivacaine (4–5 mg) plus fentanyl (20–25 mcg), followed by incremental epidural boluses. An intrathecal opioid can provide excellent long-lasting postoperative analgesia. Many anesthesiologists may not be familiar with this technique because it is not typically used for standard cesarean sections. A meta-analysis review (12 studies; $n = 693$) demonstrated that low-dose CSE (intrathecal hyperbaric bupivacaine $\leq$8 mg) required more analgesic supplementation during cesarean sections than conventional-dose CSE (>8 mg) [35]. Spinal anesthesia with a low-dose anesthetic always provides more rapid onset and may present more profound blocking effects with the possibility of sharp alterations in SVR and cardiac preload compared to epidural

anesthesia alone. Continuous spinal anesthesia is seldom performed for cesarean delivery due to the higher rate of infection, injury to nerve roots, and postdural puncture headache.

Marfan syndrome and related disorders, such as Ehlers-Danlos syndrome, are widely known to be associated with an increased risk of dural puncture and/or poor spinal anesthesia stemming from unusual feelings of loss-of-resistance, scoliosis, or dural ectasia [36].

3.4.3 Platelet Count Thresholds

Spinal/epidural hematoma is extremely rare but may cause serious and permanent neurological deficits, such as paraplegia. There is no definitive consensus regarding a lower-limit platelet count for neuraxial anesthesia in cesarean delivery to prevent spinal/epidural hematoma formation [37, 38]. In nonsurgical patients, serious spontaneous bleeding is unlikely to occur at platelet counts above $100 \times 10^3/\mu l$, and hemorrhage does not often occur until the platelet count falls below $50 \times 10^3/\mu l$. Platelet function decreases exponentially below $50 \times 10^3/\mu l$ [39–41]. Platelet counts of $80–100 \times 10^3/\mu l$, with no other coagulation abnormalities, would not increase the risk of spinal/epidural hematoma.

In addition to absolute platelet count, the decline rate in platelet numbers is probably essential. Importantly, the removal of an indwelling epidural catheter is contraindicated in patients receiving anticoagulants [42]. The use of epidural analgesia is avoided in patients needing anticoagulant therapy immediately postpartum. Rescue ECMO support, in cases of profound hemodynamic or respiratory deterioration, increases the risk of spinal/epidural hematoma.

Platelet or cryoprecipitate transfusion therapy for prompt reversal of coagulation abnormalities is likely to cause serious fluid overload complications and would not be tolerated in most parturients with CVD [38].

3.4.4 Failed Block

In cesarean section, failed neuraxial anesthesia is more common than generally recognized. The overall failure rate for general anesthesia conversion is reportedly 2.3–3.0% [43, 44]. The highest failure rate is based on estimates of labor epidural top-ups, compared to spinal or CSE procedures (4.3–5.1% versus 1.3–2.1% or 1.5–1.7%, respectively) [43, 44]. Furthermore, even after excluding "conversion to general anesthesia" cases, the breakthrough pain rate during cesarean delivery in patients receiving epidural, spinal, and CSE techniques was still 4.6% (59/1286), 1.2% (40/3224), and 4.8% (13/272), respectively [43].

Maternal emotional stress may cause hemodynamic instability or increased difficulty in establishing a new block in cesarean patients with CVD. Little can be done to save a failing block in this population. Reinstalling a new epidural is relatively contraindicated due to the toxicity risks associated with cumulative overdoses of

local anesthetic. A spinal may be the only option, though in such cases surgery must be postponed in order to allow for metabolization of the local anesthetic. However, it is extremely difficult to foresee the spinal dose required for rescuing a partial neuraxial block. A high or total spinal must be avoided in pregnant women with CVD. If time is of the essence, conversion to general anesthesia should be undertaken. However, one must remember that such emergency conversions could result in higher rates of mortality and morbidity.

3.5 General Anesthesia

General anesthetic techniques are occasionally selected for cesarean section in high-risk patients (Table 3.1). Anesthetic and vasoactive drugs should be tailored to each patient's underlying cardiopulmonary state. A carefully titrated narcotic-based anesthetic generally provides excellent hemodynamic stability throughout anesthesia. There is no convincing evidence that brief fetal exposure to general anesthetic drugs through the placenta causes irreversible neurodevelopmental issues in the neonate [45, 46]. General anesthesia has similar neonatal outcomes compared to neuraxial anesthesia [47]. Therefore, maternal hemodynamic stability should be prioritized above concerns for transient neonatal sedation and respiratory distress. Remifentanil, an ultrashort-acting opioid, may be used to decrease the risk of maternal and neonatal respiratory depression following cesarean section [48].

3.5.1 Monitoring

Arterial lines should be placed prior to induction or surgery in most patients. Central venous lines are also indicated for most patients in order to better manage hemodynamics, especially immediately after delivery, during emergency from general anesthesia, and within 12–24 h postpartum. TEE should be considered for all patients. Pulmonary artery catheter monitoring is recommended in all patients with pulmonary artery hypertension (PAH), except for those with Eisenmenger physiology or intracardiac shunt lesions. In Eisenmenger patients, large intracardiac shunts are contraindicated due to the likelihood of inaccurate cardiac output measurements. Additionally, as the difficult placement of a pulmonary artery catheter frequently causes arrhythmias, likely leading to hemodynamic instability, their use is absolutely contraindicated in such patients. A 5-lead electrocardiogram monitor and external defibrillator pads are always made ready in addition to routine standard monitors.

3.5.2 Induction

Preoperative sedation is avoided. Slowly titrated induction with opioids is an acceptable technique because there is no clear evidence that rapid sequence induction or

cricoid pressure reduces pulmonary aspiration in cesarean delivery [49, 50]. The rate of pulmonary aspiration during general anesthesia for pregnant patients may be lower than previously thought [51]. Even in neonates with a full stomach requiring emergent abdominal surgery, modified rapid sequence induction with careful mask ventilation is commonly performed without undue risk of pulmonary aspiration.

Any hypnotic agents are appropriate. Etomidate, one promising hypnotic agent, has little impact on systemic or pulmonary circulation in severe CVD patients undergoing cardiac surgery [52]. The combined use of neuromuscular rocuronium with sugammadex is performed for induction and emergence in cesarean section. Rocuronium (1.2 mg/kg) is comparably as rapid as succinylcholine in achieving optimal neuromuscular blockade for endotracheal intubation. Sugammadex can quickly reverse deep neuromuscular blockade with rocuronium. Succinylcholine has not been widely used recently.

Standard rapid-sequence induction has the obvious weakness that a mandated period of apnea is needed, which may lead to desaturation and/or atelectasis. Atelectasis in CVD parturients may cause hemodynamic instability due to afterload elevations in the pulmonary ventricle and under-filling of the systemic ventricle. Moreover, standard rapid-sequence induction is relatively contraindicated, particularly in high-risk patients (Table 3.1) when trying to attenuate stress responses to laryngoscopy and endotracheal intubation. If a rapid-sequence technique is unavoidable, especially in PH patients, deep levels of anesthesia must be rapidly achieved before intubation along with bolus injections of norepinephrine (2.5–20 mcg) in order to maintain adequate SVR. Pretreatment with lidocaine (1.0–1.5 mg/kg) and/or a short-acting beta-1 blocker (e.g., landiolol 1.25–10 mg) should be considered to minimize intubation stress. Landiolol, a beta-blocker, is more likely to possess high beta-1 selectivity and short half-life properties compared with esmolol or other beta-1 blockers. Bolus injections of landiolol have been reported to safely attenuate tachycardia in response to endotracheal intubation under general anesthesia [53, 54].

Although pregnancy is considered to increase the risk of a difficult airway, the incidence of difficult intubation in cesarean patients may not be really dissimilar from that in non-obstetric surgical patients (5.7%; 95% confidence interval (CI), 4.4–7.2% versus 5.8%; 95%CI, 4.5–7.5%, respectively) [55, 56]. The overall rate of failed intubation in cesarean section is reportedly quite low, ranging from 0 to 0.23% [55, 57, 58]. No expert anesthesiologist has experienced a failed intubation in cesarean delivery in the past decade, thanks to advances in airway management devices. For patients with an anticipated difficult airway, general anesthesia should be the first choice since conversion to general anesthesia during cesarean section is more challenging in those with CVD (Table 3.2).

3.5.3 Maintenance

If used judiciously, combinations of volatile anesthetics—along with opioids, propofol, and/or benzodiazepines—can maintain sufficient anesthetic levels to attenuate adverse hemodynamic responses. Volatile agents decrease uterine contractility

in a dose-dependent manner. Volatile agents above a minimum alveolar concentration level of 0.75 are usually avoided in patients with uterine atony. Nitrous oxide is not administrated in patients with intracardiac shunts or PH, possibly because of an increased risk of air embolization or further elevations in PVR, respectively. Hemodynamic management is described below in Sect. 3.

3.5.4 Ventilatory Strategies

Mechanical ventilation for CVD during pregnancy is managed by using the same approaches employed for the nonpregnant patient with CVD. Positive-pressure ventilation may worsen hemodynamics in some CVD patients by altering the systemic venous return, cardiac output, shunt size, shunt direction, and/or respiratory V/Q matching, all of which may adversely affect the fetus.

Maternal $PaCO_2$ is targeted within its normal range of around 28–32 mmHg in pregnancy, although short-term relative hypercapnia (e.g., around 40 mmHg) reportedly has no adverse effect on fetal or newborn well-being, according to several small clinical studies [17, 19]. To avoid lung injury, transpulmonary distending pressure (the difference between intra-alveolar and intrathoracic pressures) is more crucial than airway plateau pressure (intra-alveolar pressure). In the supine parturient, increased intrathoracic pressure, as well as decreased chest wall compliance, would theoretically allow greater plateau pressures than that of 30 cmH_2O. The latter is regarded as a maximum threshold in nonpregnant patients with lung injuries when attempting to achieve the targeted $PaCO_2$ and PaO_2 [11, 16]. Very high intrinsic positive end-expiratory pressure must be avoided. Severe respiratory acidosis and respiratory alkalosis should also be avoided since both are detrimental to the fetus due to fetal myocardial depression and decreased uteroplacental blood flow. Bicarbonate administration to mothers with marked respiratory acidosis is thought to improve fetal acidemia.

Since postsurgery mechanical ventilation has few advantages and several distinct disadvantages, the anesthesiologist must orchestrate a tracheal extubation in the operating room.

3.5.5 Emergence

Emergence from general anesthesia may cause hemodynamic deterioration in CVD patients following cesarean section. Increases in systemic ventricular preload and afterload (ventricular wall tension) may occur, potentially leading to acute systemic ventricular failure. Acute pulmonary ventricular failure might develop because of abrupt elevations in the pulmonary ventricular preload. Pulmonary atelectasis, complicated by spontaneous hypoventilation, may elevate PVR. Endotracheal tube stress, postsurgical pain, and/or emergence agitation can cause tachycardia, hypertension, and/or hypotension. Combined continuous infusions of fentanyl with alpha-2 agonist dexmedetomidine, exercising special care with regard to bradycardia, may provide smoother and faster emergence and extubation. Landiolol may

also be beneficial in attenuating the hemodynamic responses to emergence agitation and tube stress. Extubation under anesthesia may be very useful but only in some patients. It is important to ensure adequate postoperative analgesia and patient temperature and to verify reversal of the neuromuscular blockade. Postoperative nausea, vomiting, and shivering are also frequent complications that may cause hemodynamic instability in this population. The use of prophylactic antiemetics should be considered. It remains unclear whether dexmedetomidine is safe for lactation.

3.6 Hemodynamic Management

Anesthesiologists need to manage the hemodynamic changes of both the mother and the fetus, including sudden venous return induced by aortocaval decompression and uterine autotransfusion. Optimally, the anesthesiologist must maintain volume load to the systemic ventricle, heart rate with normal sinus rhythm, myocardial contractility, SVR, and respiratory conditions. Atelectasis and lung hyperinflation must be completely avoided since both may elevate PVR. The use of all-invasive monitoring and TEE may be considered.

Slow administration of oxytocin, commonly used as an uterotonic agent, is recommended to prevent oxytocin-mediated hypotension (<2 U/min) [1]. Prostaglandin F analogues and methylergonovine should be avoided as these agents may cause severe PH and coronary vasospasm. Obstetric complications, such as multiple pregnancies, pregnancy-induced hypertension, or venous thromboembolism, all impose stress on pre-existing CVD and may increase the risk of maladaptation to hemodynamic requirements. Obesity has been shown to be associated with an increased mortality risk from cardiac disease in pregnancy [1]. Obesity causes PAH or systolic and diastolic systemic ventricular dysfunction [16].

3.6.1 Arrhythmia

Many antiarrhythmic drugs, including lidocaine, have negative inotropic effects, thereby suppressing ventricular contraction in cases of severely reduced ventricular function. Inotropic agents for the treatment of acute systolic heart failure have an arrhythmogenic effect. Electrical cardioversion may be a first-line option for the treatment of a newly developed arrhythmia. Cardioversion has a very low risk of inducing fetal arrhythmias [59]. The electrode pads are placed in the anterolateral chest, with the lateral pad placed under the breast tissue [60]. Adenosine is effective in paroxysmal supraventricular tachycardia, which is the most common sustained arrhythmia in healthy pregnancy. Adenosine may frequently induce a short pause equating to cardiac standstill [59]. For pregnant women with refractory ventricular fibrillation and tachycardia, rapid infusion of amiodarone has shown more favorable outcomes than lidocaine [59, 60]. Amiodarone is prone to depress cardiac performance due to its multichannel blocking properties, which is particularly true in patients with severe ventricular failure. Temporary pacing is rarely indicated for overdrive pacing or treatment of heart block.

3.6.2 Specific Diseases

3.6.2.1 Pulmonary Arterial Hypertension

PAH (WHO Group 1) is a progressive right heart failure syndrome characterized by remodeling of the precapillary pulmonary arteries [61]. Recent small studies suggested a maternal mortality risk rate of 20–30% risk for cesarean section [62, 63]. The majority of deaths occurred within 2 weeks postpartum.

Unfortunately, no specific treatments are currently available that target the pathological mechanism of PAH: right ventricular (RV)-pulmonary arterial coupling, ventricular interaction, and RV diastolic function (see [64] for details). Therefore, anesthesiologists should consider avoiding systemic hypotension, new-onset supraventricular arrhythmias, and high output of the RV (Table 3.3). Proper prevention and treatment of supraventricular arrhythmias are absolutely crucial. The loss of atrial contractility causes deterioration of RV-arterial coupling because augmented atrial kick is a key mechanism of compensation for reduced RV stroke volume in this population. High-output RV, furthermore, likely leads to RV-arterial uncoupling because the overload of pulmonary arterial flow output may increase PAP in the latent rigid and deformable vasculature. It is, therefore, very important to avoid high output of the RV in patients with less dilated responses in the pulmonary artery to augmented pulmonary flow.

Norepinephrine (0.015–0.5 mcg/kg/min) is an initial treatment of choice because the vasopressor stimulating alpha-1, alpha-2, and beta-1 adrenergic receptors indirectly improves RV-arterial coupling with less arrhythmic complications [64]. Moreover, it decreases the ratio of systolic PAP to systolic systemic pressure. Norepinephrine can correct hypotension-associated negative interventricular interactions by both restoring optimal coronary perfusion and improving the adverse conformational ventricular shape by increased left heart ventricular afterload. In the case of sinus tachycardia induced by high-dose norepinephrine, phenylephrine, a pure alpha-1 stimulator, can be used as an alternative agent albeit while exercising great caution vis-à-vis RV exacerbation. Vasopressin is an alternative to norepinephrine. Before continuous infusions, a bolus injection should be given to determine pulmonary and systemic vascular responsiveness to such vasopressors. Other

Table 3.3 Hemodynamic goals for cesarean section in pulmonary arterial hypertension

1.	Avoid systemic hypotension: systemic diastolic pressure > 60 mmHg; sPAP/sAP <50%
2.	Avoid new-onset arrhythmias: normal sinus rhythm; HR < 100 bpm
3.	Avoid high output of the right ventricle: CI < 3.0 l/min/m^2
4.	Avoid a net positive fluid balance: use of bloodletting if required; a hemoglobin transfusion threshold of 8 g/dl except for cyanotic patients
5.	Avoid low output of the right ventricle: CI ≥ 2.0 l/min/m^2; SvO_2 > 60%; $ScvO_2$ ≥ 70%
6.	Avoid further elevations in PVR: prevention of hypoxemia (SaO_2 ≥ 90%); hypercapnia; acidosis; pain; emotional stress; hypothermia; and shivering

CI cardiac index, *HR* heart rate, *PVR* pulmonary vascular resistance, *SaO_2* arterial oxygen saturation, *sAP* systemic systolic pressure, *$ScvO_2$* central venous oxygen saturation, *SvO_2* mixed venous oxygen saturation, *sPAP* systolic pulmonary artery pressure

catecholamines (e.g., dobutamine) or pharmacological interventions for reducing RV afterload are not recommended for cesarean section in patients with PAH. Continuous intravenous infusion of nitroglycerin is relatively contraindicated in patients with uterine atony because nitroglycerin relaxes the uterine smooth muscle compared to vascular smooth muscle. Intraoperative initiation of epoprostenol or other prostacyclin derivatives should be avoided, as long as possible, due to the potential risk of systemic hypotension. Inhaled nitric oxide is a promising pulmonary vasodilator which has no effect on the fetus or on maternal systemic circulation, though it should be avoided as long as possible since once started, the patient may need to remain intubated after surgery. Since inhaled nitric oxide should be weaned gradually to avoid rebound elevations in PAP, extubation may not be possible in the operating room, and the patient may continue to need heavy sedation to facilitate endotracheal tube tolerance, which unfortunately increases the risk of RV failure. It is therefore more practical to avoid acute elevations in PVR by preventing respiratory depression or inadequate pain control, rather than directly reduce RV afterload (Table 3.3).

In general, fluid challenge may further impair RV-arterial coupling because few PAH patients with RV failure are preload-dependent. A net negative fluid balance is occasionally required (Table 3.3). Blood transfusion should also be avoided to the utmost. Patients with chronic anemia, like parturients, can generally tolerate lower hemoglobin levels. High blood viscosity generated by increased hematocrit values may worsen PAH. It remains unclear whether correction of anemia improves mortality in clinical settings. In heart failure, anemia is widely considered a surrogate marker for poor prognosis, rather than a therapeutic target [65]. Our institute suggests considering transfusion at a hemoglobin level of 8 g/dl in PAH patients undergoing cesarean section if there is neither hypovolemic hemoconcentration nor cyanotic polycythemia involved (Table 3.3). Low-dose carperitide (0.005–0.02 mcg/kg/min) or furosemide is unhesitatingly administrated if necessary. In some patients, bloodletting (drawing blood) is needed if fluid excess is present, particularly during emergence from general anesthesia.

As a last resort, dopamine or dobutamine may be used to temporarily enhance RV performance to improve RV-arterial coupling [64].

Thoracic epidural sympathectomy in PH may deteriorate RV-arterial coupling and diminish inherent compensatory RV responses to acute RV afterload elevations (i.e., homeometric adaptation to afterload without RV dilatation), thereby reducing RV contractility [66]. This finding is highly relevant in clinical settings for cesarean section in PAH patients since neuraxial anesthesia requires profound T2–T6 anesthetic levels if this procedure is to succeed. Thus, at least a T2–T3 anesthetic level may be avoided if neuraxial anesthesia is indicated in this population.

3.6.2.2 Fontan Palliation

As a growing population of adults with congenital heart disease reaches childbearing age due to improved treatments, congenital heart disease has been the most common form of CVD in pregnancy (around 70% of patients), with a profound decline in the number of rheumatic heart disease cases [67].

Single ventricle with Fontan physiology involves a parallel circulation to the pulmonary and systemic circulation, with a morphologic right or left ventricle, depending on the congenital defect. The latest form of Fontan surgery, the extracardiac technique, presents a 97% (95%CI 94–99%) survival rate at 13 years while the classical atriopulmonary connection, 76% (95%CI 67–83%) at 25 years. Long-term sequelae of Fontan circulation vary widely, including arrhythmias, worsening cyanosis from pulmonary congestion, plastic bronchitis, hepatic dysfunction, protein-losing enteropathy, pulmonary arteriovenous malformations, and/or thromboembolism [68, 69].

It is essential that Fontan circulation is able to create transpulmonary driving pressure (i.e., the difference between central venous and atrial pressures) if pulmonary blood flow is to be properly maintained. The key goals of hemodynamic management are to avoid increased PVR, sustained supraventricular arrhythmias, and increased atrioventricular valve regurgitation in order to maintain adequate driving pressure. Left uterine displacement is important for maintaining transpulmonary driving pressure in this population.

Positive-pressure ventilation is a double-edged sword. Mechanical ventilation with the use of paralysis drugs may worsen all three key goals of hemodynamic management, resulting in hemodynamic instability. On the other hand, positive-pressure ventilation may improve atrioventricular valve regurgitation by decreasing wall tension and volume load in the systemic ventricle. It may furthermore be beneficial in helping to avoid the sustained supraventricular arrhythmias caused by reduced atrial filling. In addition, positive-pressure ventilation may decrease the risk of pulmonary atelectasis which potentially worsens Fontan circulation in some patients. Similarly, while spontaneous breathing without mechanical ventilatory support (negative intrathoracic pressure) can augment blood flow to the lungs during inspiration, it may increase PVR in the case of a hypoventilation from many reasons, such as supine position with enlarged abdomen or upper airway obstruction with sedation. Emotional stress with no sedation may result in PVR elevations during cesarean section. Increased SVR should also be avoided because it is likely to increase regurgitation of the atrioventricular valve, leading to arrhythmia and/or ventricular failure.

It is, moreover, crucial that pharmacological-based therapeutic strategies aim at decreasing atrial pressure. In this way the driving pressure can be increased without raising the central venous pressure. The anesthesiologist should not hesitate to use catecholamines even before induction of anesthesia, particularly in patients with poor single ventricle and/or moderate to severe atrioventricular valve regurgitation.

In cases of unexplained hypoxia, increases in the right-to-left shunting across a fenestration or a baffle leak should always be considered a cause of desaturation. Hyperventilation, as well as increasing inspired oxygen concentrations, should be promptly applied to decrease PVR. It should be noted that overdistention of alveoli by lung hyperinflation may also cause elevated PVR, thereby increasing right-to-left shunt flow.

Although CVP monitoring is useful for managing the transpulmonary driving pressure, a central venous catheter should be removed as soon as possible after

surgery due to the high risks of thromboembolism and central vein stenosis/occlusion in Fontan physiology. External jugular vein pressure monitoring is an alternative method in most Fontan patients.

3.6.2.3 Cardiovascular Surgery with Cardiopulmonary Bypass

Aortic dissection and acquired heart valve disease have been described frequently as a main cause of cardiac death in pregnancy [1]. Therapeutic approaches to such severe diseases may require cardiovascular surgery during pregnancy under cardiopulmonary bypass (CPB) support. The mortality rate associated with CPB in pregnant patients is not higher than that in nonpregnant women [70, 71].

The major concerns surrounding CPB support are dynamic hemostatic changes—including excessive hemodilution, hypothermia (25–34 Celsius degree), and hypothermic pH management (pH-stat vs. alpha-stat)—and the release of maternal endogenous catecholamines, which adversely impact, to a severe degree, fetal well-being [72]. Moreover, total circulatory arrest (i.e., perfusion pressure remains zero) is needed in some cases. In fact, cardiovascular surgery with CPB during pregnancy is associated with a high risk of fetal loss and a fetal mortality rate of 10–20% [70, 71]. Currently, however, there is no clinical consensus regarding management of CPB in pregnancy [1, 72]. Therefore, if fetal gestational age and its condition are acceptable for cesarean section, the combined use of cardiovascular surgery with cesarean section is recommended.

Our standard practice is that cesarean section is performed under general anesthesia in the cardiac operating room, followed immediately by cardiovascular surgery with CPB. During the cardiovascular procedure, the abdominal surgical wound is packed with the uterine incision closed. The abdominal wound is finally closed after chest closure. As median sternotomy or CPB institution can be performed simultaneously during the cesarean section procedure, determining the optimal timing of these procedures can only be made on a case-by-case basis. Unfractionated heparin and protamine, both commonly used in CPB management, do not cross the placenta.

3.6.2.4 Maternal Cardiac Transplant

Pregnant patients with normal ventricular function and no evidence of allograft rejection are regarded as a low-risk class (Table 3.1) since they present no significant complications in terms of hemodynamic management. As the recipient heart is denervated, the recipient's cardiac output is preload-dependent. Atropine, a vagolytic drug, is ineffective at treating bradycardia. Neuraxial anesthesia-induced sympathectomy does not induce bradycardia. Following cardiac transplantation, two P waves are typically seen on an electrocardiogram when using the standard biatrial anastomosis technique, though the native P wave has no effect on the chronotropic activity of the transplanted heart. Cardiac allograft vasculopathy is one of the major causes of late-stage heart failure, which involves diffuse narrowing of the coronary arteries. The recipient often does not experience myocardial ischemic pain due to the denervated heart. It should be noted that myocardial ischemia might occur without any clinical symptoms of pain in long-term recipients.

3.6.3 Cardiopulmonary Resuscitation

Anesthesia-related complications still account for approximately 8% of maternal cardiac arrests during hospitalization for delivery [73]. A standard cardiopulmonary resuscitation (CPR) procedure is recommended for pregnant women with/without CVD [60]. The electrical energy required for defibrillation remains unchanging throughout all stages of pregnancy. Anterolateral pads should be kept on hand as with nonpregnant resuscitation.

Three key points for CPR in pregnant patients are manual displacement of the uterus to the left, which would relieve aortocaval compression, early initiation of ventilatory support that would counteract reduced maternal oxygen reserves, and possible resort to a perimortem cesarean section procedure. If circulation cannot be restored within 5 min, perimortem delivery is generally recommended, although it is unclear whether such delivery is associated with an increased successful resuscitation rate.

3.7 Postoperative Management

Patients should be carefully monitored in a cardiac intensive care unit in the first few days following surgery because of the high risk for sudden death. The anticipation and prevention of adverse events are essential for successful postoperative management.

3.7.1 Hemodynamic Management

A net fluid balance is typically maintained at around zero for 6–12 h after surgery in most patients. Spinal anesthesia alone for surgery carries the risk of developing heart failure and/or pulmonary edema if abrupt resolution of the sympathectomy coincides with physiological fluid volume expansion postpartum (Table 3.2). Aggressive diuretic therapy should be considered to prevent a positive fluid balance. Venous congestion is the major risk factor signaling worsening renal function in patients with advanced heart failure [74, 75]. Antiemetic drugs are generally indicated. The usual oral medications, including anticoagulants, should be restarted as soon as possible. Early ambulation and mechanical prophylactic treatment (e.g., elastic support stockings) are important to prevent a thromboembolic event.

3.7.2 Postoperative Analgesia

Patients may benefit from intrathecal opioid use for surgery and/or continuous epidural analgesia for postoperative analgesia (Table 3.2). For postpartum analgesia following general anesthesia, opioid infusion therapy is administered to CVD patients after cesarean delivery. Commonly used is the bilateral transversus abdominis plane (TAP) block, a T6-L1 regional block technique, as it significantly reduces

systemic opioid requirements in this population [76]. The TAP block can usually be performed in patients on anticoagulant treatment, though it requires about 3–5 times more volume of local anesthetic compared to standard epidural analgesia.

3.8 Conclusion

Cardiovascular patients undergoing cesarean section pose profound anesthetic challenges. The majority of cesarean deliveries tend to be performed under neuraxial anesthesia in this population. Currently, however, no definitive clinical data exists with regard to which subsets of patients should receive neuraxial versus general anesthesia for this procedure. The need for obstetric general anesthesia will continue far into the foreseeable future. Anesthesiologists must continually work to sharpen general anesthetic skill levels and strategies for pregnant patients with CVD. Until evidence from well-designed clinical trials becomes available, anesthetic management for this population should be left to the discretion of the anesthesiologist and patient in conjunction with an expert multidisciplinary team.

References

1. European Society of Gynecology (ESG), Association for European Pediatric Cardiology (AEPC), German Society for Gender Medicine (DGesGM) et al (2011) ESC Guidelines on the management of cardiovascular diseases during pregnancy: the task force on the management of cardiovascular diseases during pregnancy of the European Society of Cardiology (ESC). Eur Heart J 32:3147–3197
2. Elkayam U, Goland S, Pieper PG et al (2016) High-risk cardiac disease in pregnancy: Part I. J Am Coll Cardiol 68:396–410
3. Siu SC, Sermer M, Colman JM et al (2001) Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation 104:515–521
4. Khairy P, Ouyang DW, Fernandes SM et al (2006) Pregnancy outcomes in women with congenital heart disease. Circulation 113:517–524
5. Hilfiker-Kleiner D, Haghikia A, Nonhoff J et al (2015) Peripartum cardiomyopathy: current management and future perspectives. Eur Heart J 36:1090–1097
6. Meschia G (2011) Fetal oxygenation and maternal ventilation. Clin Chest Med 32:15–19
7. Zeeman GG, Hatab M, Twickler DM (2003) Maternal cerebral blood flow changes in pregnancy. Am J Obstet Gynecol 189:968–972
8. Nevo O, Soustiel JF, Thaler I (2010) Maternal cerebral blood flow during normal pregnancy: a cross-sectional study. Am J Obstet Gynecol 203:475.e1–475.e6
9. Ikeda T, Ikenoue T, Mori N et al (1993) Effect of early pregnancy on maternal regional cerebral blood flow. Am J Obstet Gynecol 168:1303–1308
10. Lapinsky SE, Kruczynski K, Slutsky AS (1995) Critical care in the pregnant patient. Am J Respir Crit Care Med 152:427–455
11. Campbell LA, Klocke RA (2001) Implications for the pregnant patient. Am J Respir Crit Care Med 163:1051–1054
12. Grindheim G, Toska K, Estensen ME et al (2012) Changes in pulmonary function during pregnancy: a longitudinal cohort study. BJOG 119:94–101
13. McAuliffe F, Kametas N, Costello J et al (2002) Respiratory function in singleton and twin pregnancy. BJOG 109:765–769

14. Hegewald MJ, Crapo RO (2011) Respiratory physiology in pregnancy. Clin Chest Med 32:1–13
15. Douglas MJ (2001) Platelets, the parturient and regional anesthesia. Int J Obstet Anesth 10:113–120
16. Lapinsky SE, Posadas-Calleja JG, McCullagh I (2009) Clinical review: Ventilatory strategies for obstetric, brain-injured and obese patients. Crit Care 13:206
17. Fraser D, Jensen D, Wolfe LA (2008) Fetal heart rate response to maternal hypocapnia and hypercapnia in late gestation. J Obstet Gynaecol Can 30:312–316
18. Reitman E, Flood P (2011) Anaesthetic considerations for non-obstetric surgery during pregnancy. Br J Anaesth 107(Suppl 1):i72–i78
19. Ivankovic AD, Elam JO, Huffman J (1970) Effect of maternal hypercarbia on the newborn infant. Am J Obstet Gynecol 107:939–946
20. Polvi HJ, Pirhonen JP, Erkkola RU (1995) The hemodynamic effects of maternal hypo- and hyperoxygenation in healthy term pregnancies. Obstet Gynecol 86:795–799
21. Maxwell BG, El-Sayed YY, Riley ET et al (2013) Peripartum outcomes and anaesthetic management of parturients with moderate to complex congenital heart disease or pulmonary hypertension. Anaesthesia 68:52–59
22. Langesaeter E, Dragsund M, Rosseland LA (2010) Regional anaesthesia for a caesarean section in women with cardiac disease: a prospective study. Acta Anaesthesiol Scand 54:46–54
23. Ioscovich AM, Goldszmidt E, Fadeev AV et al (2009) Peripartum anesthetic management of patients with aortic valve stenosis: a retrospective study and literature review. Int J Obstet Anesth 18:379–386
24. Weiss BM, Zemp L, Seifert B et al (1998) Outcome of pulmonary vascular disease in pregnancy: a systematic overview from 1978 through 1996. J Am Coll Cardiol 31:1650–1657
25. Lewis NL, Dob DP, Yentis SM (2003) UK registry of high-risk obstetric anaesthesia: arrhythmias, cardiomyopathy, aortic stenosis, transposition of the great arteries and Marfan's syndrome. Int J Obstet Anesth 12:28–34
26. Ngan Kee WD (2010) Prevention of maternal hypotension after regional anaesthesia for caesarean section. Curr Opin Anaesthesiol 23:304–309
27. Mercier FJ (2011) Fluid loading for cesarean delivery under spinal anesthesia: have we studied all the options? Anesth Analg 113:677–680
28. Maayan-Metzger A, Schushan-Eisen I, Todris L et al (2010) Maternal hypotension during elective cesarean section and short-term neonatal outcome. Am J Obstet Gynecol 202:56.e1–56.e5
29. Laudenbach V, Mercier FJ, Rozé JC et al (2009) Anaesthesia mode for caesarean section and mortality in very preterm infants: an epidemiologic study in the EPIPAGE cohort. Int J Obstet Anesth 18:142–149
30. Moore SA, Dietl CA, Coleman DM (2016) Extracorporeal life support during pregnancy. J Thorac Cardiovasc Surg 151:1154–1160
31. Ng K, Parsons J, Cyna AM et al (2004) Spinal versus epidural anaesthesia for caesarean section. Cochrane Database Syst Rev 2:CD003765
32. Kasaba T, Onizuka S, Takasaki M (2003) Procaine and mepivacaine have less toxicity in vitro than other clinically used local anesthetics. Anesth Analg 97:85–90
33. Hamlyn EL, Douglass CA, Plaat F et al (2005) Low-dose sequential combined spinal-epidural: an anaesthetic technique for Caesarean section in patients with significant cardiac disease. Int J Obstet Anesth 14:355–361
34. Roofthooft E, Van de Velde M (2008) Low-dose spinal anaesthesia for Caesarean section to prevent spinal-induced hypotension. Curr Opin Anaesthesiol 21:259–262
35. Arzola C, Wieczorek PM (2011) Efficacy of low-dose bupivacaine in spinal anaesthesia for Caesarean delivery: systematic review and meta-analysis. Br J Anaesth 107:308–318
36. Baghirzada L, Krings T, Carvalho JC (2012) Regional anesthesia in Marfan syndrome, not all dural ectasias are the same: a report of two cases. Can J Anaesth 59:1052–1057
37. Henke VG, Bateman BT, Leffert LR (2013) Spinal anesthesia in severe preeclampsia. Anesth Analg 117:686–693

38. Estcourt LJ, Ingram C, Doree C et al (2016) Use of platelet transfusions prior to lumbar punctures or epidural anaesthesia for the prevention of complications in people with thrombocytopenia. Cochrane Database Syst Rev 24:CD011980
39. Norfolk DR, Ancliffe PJ, Contreras M et al (1998) Consensus Conference on Platelet Transfusion, Royal College of Physicians of Edinburgh, 27-28 November 1997. Synopsis of background papers. Br J Haematol 101:609–617
40. Stainsby D, MacLennan S, Hamilton PJ (2000) Management of massive blood loss: a template guideline. Br J Anaesth 85:487–491
41. Samama CM, Djoudi R, Lecompte T et al (2005) Perioperative platelet transfusion: recommendations of the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSaPS) 2003. Can J Anaesth 52:30–37
42. Horlocker TT, Wedel DJ, Rowlingson JC et al (2010) Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). Reg Anesth Pain Med 35:64–101
43. Kinsella SM (2008) A prospective audit of regional anaesthesia failure in 5080 Caesarean sections. Anaesthesia 63:822–832
44. Bloom SL, Spong CY, Weiner SJ et al (2005) Complications of anesthesia for cesarean delivery. Obstet Gynecol 106:281–287
45. Sun L (2010) Early childhood general anaesthesia exposure and neurocognitive development. Br J Anaesth 105(Suppl 1):i61–i68
46. Sun LS, Li G, Miller TL et al (2016) Association between a single general anesthesia exposure before age 36 months and neurocognitive outcomes in later childhood. JAMA 315:2312–2320
47. Afolabi BB, Lesi FE (2012) Regional versus general anaesthesia for Caesarean section. Cochrane Database Syst Rev 10:CD004350
48. Kan RE, Hughes SC, Rosen MA et al (1998) Intravenous remifentanil: placental transfer, maternal and neonatal effects. Anesthesiology 88:1467–1474
49. Neilipovitz DT, Crosby ET (2007) No evidence for decreased incidence of aspiration after rapid sequence induction. Can J Anaesth 54:748–764
50. Algie CM, Mahar RK, Tan HB et al (2015) Effectiveness and risks of cricoid pressure during rapid sequence induction for endotracheal intubation. Cochrane Database Syst Rev 11:CD011656
51. Dean G, Jacobs AR, Goldstein RC et al (2011) The safety of deep sedation without intubation for abortion in the outpatient setting. J Clin Anesth 23:437–442
52. Wagner CE, Bick JS, Johnson D et al (2014) Etomidate use and postoperative outcomes among cardiac surgery patients. Anesthesiology 120:579–589
53. Suehiro K, Okutani R (2011) Landiolol attenuates cardiovascular response at induction of general anesthesia for cesarean delivery. J Anesth 26:200–205
54. Sugiura S, Seki S, Hidaka K et al (2007) The hemodynamic effects of landiolol, an ultrashort-acting beta1-selective blocker, on endotracheal intubation in patients with and without hypertension. Anesth Analg 104:124–129
55. McKeen DM, George RB, O'Connell CM et al (2011) Difficult and failed intubation: incident rates and maternal, obstetrical, and anesthetic predictors. Can J Anaesth 58:514–524
56. Shiga T, Wajima Z, Inoue T et al (2005) Predicting difficult intubation in apparently normal patients: a meta-analysis of bedside screening test performance. Anesthesiology 103:429–437
57. Djabatey EA, Barclay PM (2009) Difficult and failed intubation in 3430 obstetric general anaesthetics. Aaesthesia 64:1168–1171
58. Kinsella SM, Winton AL, Mushambi MC et al (2015) Failed tracheal intubation during obstetric general anaesthesia: a literature review. Int J Obstet Anesth 24:356–374
59. Enriquez AD, Economy KE, Tedrow UB (2014) Contemporary management of arrhythmias during pregnancy. Circ Arrhythm Electrophysiol 7:961–967
60. Jeejeebhoy FM, Zelop CM, Lipman S et al (2015) Cardiac arrest in pregnancy: a scientific statement from the American Heart Association. Circulation 132:1747–1773
61. McLaughlin VV, Shah SJ, Souza R et al (2015) Management of pulmonary arterial hypertension. J Am Coll Cardiol 65:1976–1997

62. Bédard E, Dimopoulos K, Gatzoulis MA (2009) Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? Eur Heart J 30:256–265
63. Jaïs X, Olsson KM, Barbera JA (2012) Pregnancy outcomes in pulmonary arterial hypertension in the modern management era. Eur Respir J 40:881–885
64. Naeije R, Manes A (2014) The right ventricle in pulmonary arterial hypertension. Eur Respir Rev 23:476–448
65. Swedberg K, Young JB, Anand IS et al (2013) Treatment of anemia with darbepoetin alfa in systolic heart failure. N Engl J Med 368:1210–1219
66. Rex S, Missant C, Segers P et al (2007) Thoracic epidural anesthesia impairs the hemodynamic response to acute pulmonary hypertension by deteriorating right ventricular-pulmonary arterial coupling. Crit Care Med 35:222–229
67. Brickner ME (2014) Cardiovascular management in pregnancy: congenital heart disease. Circulation 130:273–282
68. d'Udekem Y, Iyengar AJ, Galati JC et al (2014) Redefining expectations of long-term survival after the Fontan procedure: twenty-five years of follow-up from the entire population of Australia and New Zealand. Circulation 130:S32–S38
69. Emani SM, del Nido PJ (2013) Strategies to maintain biventricular circulation in patients with high-risk anatomy. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 16:37–42
70. Rajagopalan S, Nwazota N, Chandrasekhar S (2014) Outcomes in pregnant women with acute aortic dissections: a review of the literature from 2003 to 2013. Int J Obstet Anesth 23:348–356
71. John AS, Gurley F, Schaff HV et al (2011) Cardiopulmonary bypass during pregnancy. Ann Thorac Surg 91:1191–1196
72. Chandrasekhar S, Cook CR, Collard CD (2009) Cardiac surgery in the parturient. Anesth Analg 108:777–785
73. Mhyre JM, Tsen LC, Einav S et al (2014) Cardiac arrest during hospitalization for delivery in the United States. Anesthesiology 120:810–818
74. Mullens W, Abrahams Z, Francis GS et al (2009) Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol 53:589–596
75. Hanberg JS, Sury K, Wilson FP et al (2016) Reduced cardiac index is not the dominant driver of renal dysfunction in heart failure. J Am Coll Cardiol 67:2199–2208
76. Mishriky BM, George RB, Habib AS (2012) Transversus abdominis plane block for analgesia after Cesarean delivery: a systematic review and meta-analysis. Can J Anaesth 59:766–778

Postpartum Management

4

Chizuko Aoki-Kamiya

Abstract

For several days after delivery, the maternal circulatory dynamics change very dramatically. The venous return increases immediately after child and placental expulsion due to rapid uterine contractions, while bleeding and vascular permeability are increased due to the delivery. This balance determines the circulating plasma volume right after delivery. For several days, diuresis decreases, vascular permeability becomes normal, and fluid stored in the third space returns to the blood vessels. Therefore, the circulating plasma volume in many cases reaches a peak several days after delivery. Immediately after delivery, there is a risk of severe obstetric bleeding, and thromboembolism can easily develop due to accelerated blood coagulation. Since the maternal death often occur within 1 week after delivery, careful attention during this period is required especially for women with severe heart disease.

Peripartum cardiocirculatory changes are considered to persist up to 3–6 months after delivery. There are almost no reports on the effects of the risks of child-rearing, including breast-feeding, on mothers with cardiovascular disease. Several studies suggested that hormones related to lactation, such as oxytocin and prolactin, might be possible pathogenetic factors of postpartum aortic dissection and peripartum cardiomyopathy. In addition, it was also reported that the risk of a cardiac event would be highest in the postpartum period in women with long QT syndrome.

Keywords

Puerperium · Lactation · Medication · Prognosis

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4.1 The Immediate Puerperium Management

Along with the rapid uterine contraction immediately after delivery, the pressure on the inferior vena cava, which was caused by the enlarged uterus in the second half of the pregnancy, is released, leading to a drastic increase of venous flow. Cardiac output reaches at the highest level (at ~1.8 times as prepregnancy level) just after newborn and placental delivery [1]. Therefore, physicians should pay attention to complications such as the rapid development of heart failure or aortic dissection or pulmonary hypertensive crisis.

There has been little known about changes in circulating plasma volume during immediate puerperium on a day-to-day basis. Interestingly, brain natriuretic peptide (BNP) levels were found to become highest on day 3 after delivery [2]. A case with aortic regurgitation and implantable cardioverter-defibrillator (ICD) indicated that the ICD's stored fluid index gradually increased and exceeded the threshold on the eighth day after delivery (Fig. 4.1) [3]. She was treated with diuretics and recovered from postpartum heart failure. Although there are differences between individuals, the circulating plasma volume causes transient volume overload after delivery and takes about 4–6 weeks or longer to return to normal.

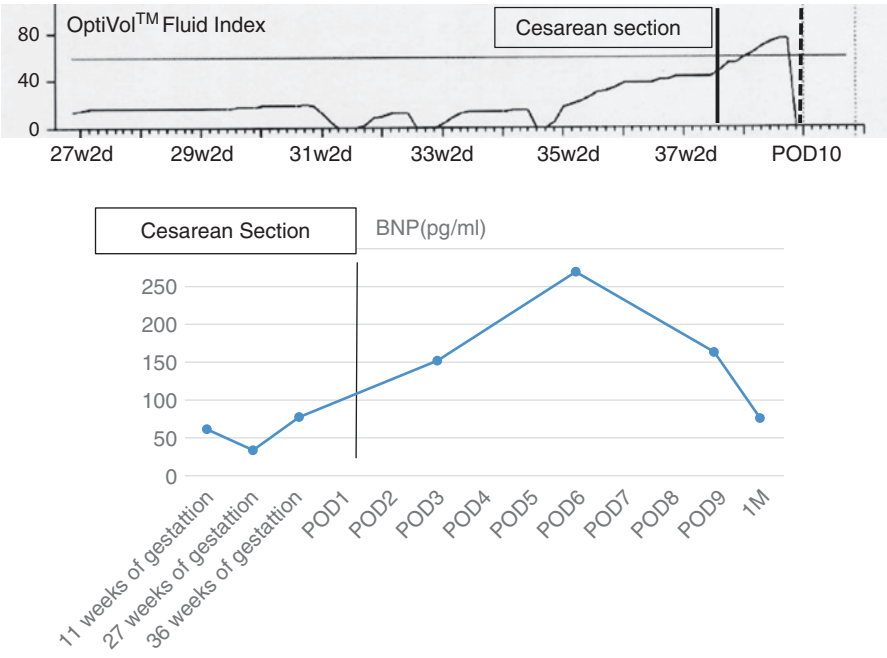

Fig. 4.1 Fluid assessment based on the intrathoracic impedance monitoring in a peripartum woman with aortic regurgitation [3]. A woman after aortic valve replacement with biological valve and implantable cardioverter-defibrillators' implantation for the episode of ventricular fibrillation delivered by Caesarean section. The total amount of bleeding was 540 ml. After delivery, she gained weight again with worsen bilateral peripheral edema, and her BNP level was increased. The OptiVol™ fluid index got out of the peak at postoperative 8 days. She was treated with diuretics and recovered from postpartum heart failure. *BNP* brain natriuretic peptide, *POD* postoperative day

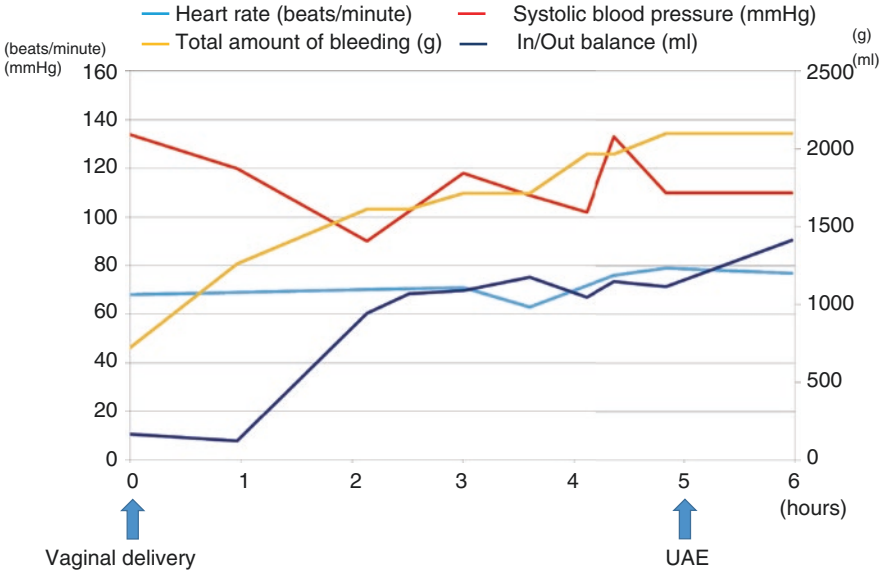

Fig. 4.2 Vital signs at atonic bleeding in a woman after Jatene operation for transposition of the great arteries. A woman after Jatene operation for transposition of the great arteries delivered her baby under epidural anesthesia. Total amount of intrapartum hemorrhage was 720 g. More bleeding (542 g) was observed for the first 1 h after delivery. She complained about feeling bad and total amount of bleeding became more than 1500 g after 2 h from delivery. Her hemoglobin levels were decreased from 11.6 to 7.4 g/dl. Finally she was proceeded with uterine artery embolization. In the course of peripartum hemorrhage, her heart rates did not increased and kept around 70 beats/min. *UAE* uterine artery embolization

Massive intrapartum hemorrhage is a life-threatening event, and elevated heart rate is one of the indicators of excessive bleeding, such as shock index. However, some women with bradyarrhythmia and/or cardiovascular disease cannot increase their heart rate with massive bleeding (Fig. 4.2). Obstetricians and midwives should take caution with such patients.

The risk of thrombosis is significantly increased in the puerperium. Especially, women after Caesarean section are faced with a high risk of deep vein thrombosis and pulmonary embolism. Women at high risk must acquire the prevention of thrombosis, such as the administration of anticoagulants and taking compression stockings.

4.2 The Late Puerperium Management

Since physical changes in a pregnant woman are noticeably significant, family members and people in her presence should help her by carrying her packages, giving her a place to sit when needed, being careful not to bump into her, etc. On the other hand, since her appearance returns to normal after delivery, some people may not recognize that she is mainly caring for her newborn baby and is still in need of support due to her fragile health condition. Although the World Health Organization (WHO)

reported that during the puerperal period, there is a higher risk for an increased maternal death rate, the mother's health needs are usually neglected in this period [4]. Careful attention should be paid during the puerperal period to the mother's body due to the large circulatory changes, as well as to the heavy demands of child-rearing.

A study of maternal death in the UK (United Kingdom) reported that 13% of late maternal deaths confirmed from the 6th week to 1 year after delivery were caused by cardiac conditions, including acute myocardial infarction, cardiac myopathy, sudden arrhythmic death syndrome (SADS), aortic dissection, etc. [5]. The highest event risk was observed during the 9 months after delivery especially in women with LQT [6, 7]. A Japanese study of 126 women with LQT that was confirmed by a genetic test reported that postpartum LQT was prolonged, compared to that during pregnancy, with development of many cardiac events. Furthermore, development of postpartum events was confirmed even in the women who took oral β-blockers [7]. For high-risk cases, oral β-blockers and implantation of an ICD are considered beneficial. In addition, it is recommended that follow-up observation of women with peripartum cardiomyopathy and with other diseases using of a wearable cardiac-defibrillator should be provided for some time after delivery [8]. This is especially important when the effects of pregnancy/delivery may play a major role in the development of an arrhythmia.

4.3 Breast-Feeding and Cardiovascular Disease

4.3.1 Physiology of Breast-Feeding

After delivery, the breasts start to secrete colostrum, which contains more minerals and protein, including antibodies such as immunoglobulin A, but less sugar and fat. Colostrum has a preventive effect for neonates against infectious disease. A month later, a nursing mother produces 500–700 ml of milk daily and needs at least +350 kcal and +800–1000 ml water intake. Breast-feeding prolactin, which belongs to the growth hormone family, is essential for lactation. Although plasma prolactin levels fall after delivery to levels lower than during pregnancy, each act of sucking triggers a rise in levels. Oxytocin also stimulates milk expression.

Breast-feeding in sitting or reclining position costs about 2 Mets (metabolic equivalents). Other child care activities, such as dressing and bathing, cost 2–3 Mets, which are equal to occupations with light to moderate effort [9].

4.3.2 Breast-Feeding and Cardiovascular Disease

Although breast-feeding has many merits, including transfer of immunity and development of mother-infant affection, some mothers with severe cardiac disease may complain of fatigue caused by breast-feeding, which increases their basal metabolic rate. In addition, there are growing concerns about the effects of hormones involved in lactation on disease conditions which may be aggravated in the puerperium period (e.g., peripartum cardiomyopathy and aortic dissection in patients with Marfan's syndrome [see also Chap. 11 and 13]).

Conventionally, it is known that complications of cardiac failure frequently develop in pregnant women with organic heart disease before and after the 30th week of pregnancy when the circulating plasma volume increases, while many women with peripartum cardiomyopathy are diagnosed with having cardiac failure after delivery. Based on this difference in the timing of increased incidence of cardiac failure, it has been recently suggested that prolactin may be involved in cardiac disease. In 2007, Hilfiker-Kleiner et al. reported that the mechanism of cardiomyopathy/cardiac failure, which occurs at a high rate in female mice model, involved an increase in intramyocardial oxidant stress after pregnancy/delivery [10]. An increase in intramyocardial oxidant stress induces increased cathepsin D activity, a proteolytic enzyme. This proteolytic enzyme cleaves prolactin, a galactopoietic hormone that is high in blood during the perinatal period. The cleaved prolactin (prolactin fragments) inhibits angiogenesis and other angiopathic properties, and thus prolactin is considered to be involved in the development of cardiomyopathy. In addition, it was also reported that mice which became pregnant and delivered after administration of bromocriptine, an anti-prolactin drug, did not develop cardiomyopathy. Furthermore, cardiomyopathy could be prevented when bromocriptine was administered to women with a history of peripartum cardiomyopathy during their subsequent pregnancy, because cleaved prolactin is present in the serum of patients with peripartum cardiomyopathy. Based on these findings, anti-prolactin treatment has recently been used as a new disease-specific therapy [11, 12].

4.3.3 Breast-Feeding and Medication

Passive diffusion and carrier-mediated transport by a transporter, etc. are involved in drug transfer via breast-feeding. Drug properties related to passive diffusion include protein binding and the ionization and hydrophobic properties. Therefore, basic drugs with a lower protein binding affinity and a higher lipophilicity are elevated in breast milk. Thus, a hydrophilic acid drug with a low protein binding affinity should be selected when similar acting drugs are available. However, most drugs are considered to be safe because an extremely small amount of a drug is transferred via breast milk, compared to the dose of the drug used in the therapy. A recent database of drug safety for breast-feeding is available through the Internet. Both the Japan Drug Information Institute in Pregnancy (https://www.ncchd.go.jp/kusuri/lactation/index.html) and LactMed (https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm) in the USA are useful sources of information.

4.4 Impact of Pregnancy on Long-Term Outcomes

So far, many reports have discussed the prognosis for women with cardiac disease during a relatively short period from pregnancy to immediately after delivery. However, it has not been clarified how pregnancy/delivery, which drastically changes the circulatory dynamics, would affect women with cardiac disease in the long term.

It is suggested that peripartum cardiac stress resulted in deterioration of the New York Heart Association (NYHA) cardiac functional classification, progressive enlargement and dysfunction of the right ventricle, and an increase of tricuspid regurgitation in patients who underwent either Senning or the Mustard procedure for correction of transposition of the great arteries [13]. Therefore, it was considerable that pregnancy affects the long-term prognosis in women with a systemic right ventricle. In addition, in a study with patients who underwent a repair of tetralogy of Fallot, it was found that right ventricular enlargement tended to progress after successive pregnancies/deliveries [14–16]. This tendency was significant especially in patients whose right ventricular enlargement had progressed even before pregnancy [16] (see Chap. 14). Therefore, the necessity for intervention to the pulmonary valve before pregnancy should be discussed with patients having right ventricular enlargement associated with severe pulmonary valve regurgitation.

Even in the women with Marfan's syndrome, pregnancy/delivery is a factor that significantly affects long-term aortic events. The risk factors for successive aortic events include women with greater aortic diameter, rapid aortic dilation upon or during pregnancy, increased number of pregnancies, no use of β-blockers during pregnancy, and no prospective follow-up observation after pregnancy [17].

Approaches initiated before both pregnancy and perinatal management will be required not only for a safe pregnancy/delivery but also for the best long-term prognosis.

4.5 Relations Between Peripartum and Later Cardiovascular Events

Women with cardiac disease, who were complicated with peripartum cardiovascular events, are likely to have another cardiovascular event in the early phase after delivery [18, 19]. Considering a perinatal event as a warning sign, physicians should carefully perform puerperal follow-up observations on women with a perinatal event. Pregnancy is a stress test for life—it is important to pass down the lessons obtained in the perinatal period from the department of obstetrics to the physicians in charge of the successive follow-up observation.

References

1. Robson SC, Dunlop W, Boys RJ, Hunter S (1987) Cardiac output during labour. Br Med J 295:1169–1172
2. Yoshimura T, Yoshimura M, Yasue H et al (1994) Plasma concentration of atrial natriuretic peptide and brain natriuretic peptide during normal human pregnancy and the postpartum period. J Endocrinol 140:393–397
3. Daimon A, Kamiya AC, Sawada M et al (2018) Utility of fluid assessment based on the intrathoracic impedance monitoring in a peripartum woman with heart disease. Int Heart J 59:435–438
4. World Health Organization (2013) WHO recommendations on postnatal care of the mother and newborn. WHO Library Cataloguing-in-Publication Data, Geneva. ISBN 978-92-4-150664-9

5. Knight M, Tuffnell D, Kenyon S, Shakespeare J, Gray R, Kurinczuk JJ (Eds.) on behalf of MBRRACE-UK (2015) In: Saving lives, improving mothers' care - surveillance of maternal deaths in the UK 2011–13 and lessons learned to inform maternity care from the UK and Ireland confidential enquiries into maternal deaths and morbidity 2009–13. National Perinatal Epidemiology Unit, University of Oxford, Oxford. ISBN 978-0-9931267-3-4
6. Seth R, Moss AJ, McNitt S et al (2007) Long QT syndrome and pregnancy. J Am Coll Cardiol 49:1092–1098
7. Ishibashi K, Aiba T, Kamiya C et al (2017) Arrhythmia risk and β-blocker therapy in pregnant women with long QT syndrome. Heart 103:1374–1379
8. Duncker D, Haghikia A, König T et al (2014) Risk for ventricular fibrillation in peripartum cardiomyopathy with severely reduced left ventricular function-value of the wearable cardioverter/defibrillator. Eur J Heart Fail 16:1331–1336
9. Ainsworth BE, Haskell WL, Herrmann SD et al (2011) 2011 compendium of physical activities: a second update of codes and MET values. Med Sci Sports Exerc 43:1575–1581
10. Hilfiker-Kleiner D, Kaminski K, Podewski E et al (2007) A cathepsin D-cleaved 16 kDa form of prolactin mediates postpartum cardiomyopathy. Cell 128:589–600
11. Sliwa K, Blauwet L, Tibazarwa K et al (2010) Evaluation of bromocriptine in the treatment of acute severe peripartum cardiomyopathy: a proof-of-concept pilot study. Circulation 121:1465–1473
12. Hilfiker-Kleiner D, Haghikia A, Berliner D et al (2017) Bromocriptine for the treatment of peripartum cardiomyopathy: a multicentre randomized study. Eur Heart J 35:2671–2679
13. Guedes A, Mercier LA, Leduc L et al (2004) Impact of pregnancy on the systemic right ventricle after a Mustard operation for transposition of the great arteries. J Am Coll Cardiol 44:433–437
14. Uebing A, Arvanitis P, Li W et al (2010) Effect of pregnancy on clinical status and ventricular function in women with heart disease. Int J Cardiol 139:50–59
15. Kamiya CA, Iwamiya T, Neki R et al (2012) Outcome of pregnancy and effects on the right heart in women with repaired tetralogy of fallot. Circ J 76:957–963
16. Egidy Assenza G, Cassater D, Landzberg M et al (2013) The effects of pregnancy on right ventricular remodeling in women with repaired tetralogy of Fallot. Int J Cardiol 168:1847–1852
17. Donnelly RT, Pinto NM, Kocolas I, Yetman AT (2012) The immediate and long-term impact of pregnancy on aortic growth rate and mortality in women with Marfan syndrome. J Am Coll Cardiol 60:224–229
18. Balint OH, Siu SC, Mason J et al (2010) Cardiac outcomes after pregnancy in women with congenital heart disease. Heart 96(20):1656–1661
19. Kampman MAM, Balci A, Groen H et al (2015) Cardiac function and cardiac events 1-year postpartum in women with congenital heart disease. Am Heart J 169(2):298–304

Preconception Counseling and Contraception

5

Chizuko Aoki-Kamiya

Abstract

Circulatory dynamics markedly change throughout pregnancy and delivery. While many women with heart disease deliver safely, some diseases and pathological conditions are life-threatening and high risks for both mother and fetus. Thus, preconception counseling is important for safety of women with cardiovascular disease, and it is preferable to start counseling from the teenage years among women with congenital heart disease. The specialized multidisciplinary medical team, including obstetrics, adult and pediatric cardiology, anesthesiology, cardiac surgery, genetic clinic, and neonatology, is essential for high-risk pregnancy, and involvement of the team is also important in preconception counseling. Teenage years are the same timing of transitional care. As a prerequisite of counseling, it is necessary to identify whether the patient sufficiently understands their own disease and symptoms, and it is preferable to begin with an explanation of these issues when understanding is insufficient. It is important to offer the safe contraception for women with heart disease, who do not want to get pregnant, since some contraception increase the risk of thromboembolism.

Keywords

Pregnancy risk · Counseling · Transitional care · Contraception

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5.1 Overview of Preconception Counseling

Overview of preconception counseling is shown in Fig. 5.1. In women with congenital heart disease (CHD), preconception counseling is preferable to start counseling from the teenage years, which is almost the same timing of transitional care. As a prerequisite of counseling, it is necessary to identify whether the patient sufficiently understands their own disease and symptoms, and it is preferable to begin with an explanation of these issues when understanding is insufficient. Then, physiological changes and estimated risks of maternal complication in the perinatal period and long-term outcome should be explained and discussed in an understandable way. If the patient wishes pregnancy for real, more detailed information such as expected course of pregnancy and fetal risks should be added. For women who do not want to become pregnant, instructions on contraception and prescription of contraceptives are necessary.

5.2 Risk Assessment of Pregnancy with Cardiovascular Disease

5.2.1 Risk Classification and Scoring Systems

Three main methods are used to assess the risk of pregnancy with cardiovascular disease. The first was prepared by modifying the World Health Organization (WHO) contraception risk classification for women with concomitant heart disease [1] for pregnancy and delivery (modified WHO classification). Each cardiovascular disease is classified into four groups: WHO class 1 (risk no higher than general population), WHO class 2 (small increased risk of maternal mortality and

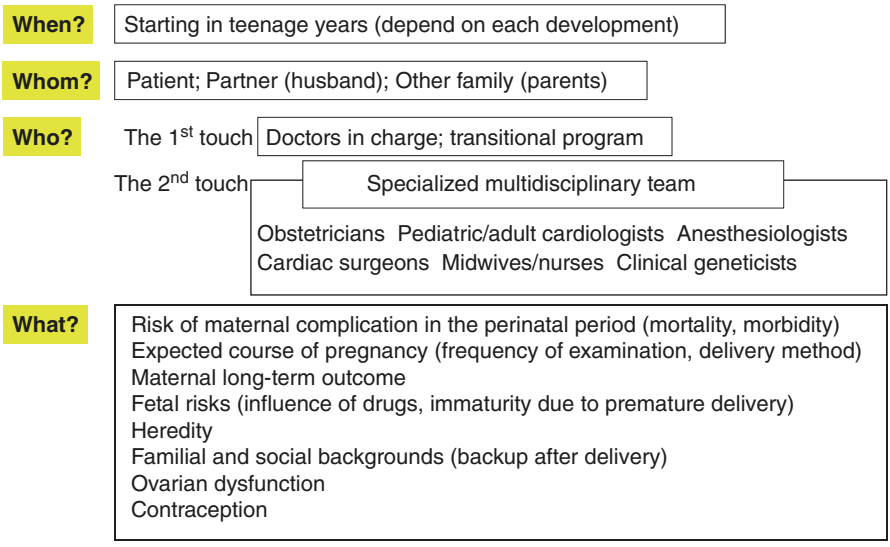

Fig. 5.1 Overview of preconception counseling

morbidity), WHO class 3 (significant increased risk of maternal mortality and morbidity; expert cardiac and obstetric pre-pregnancy, antenatal and postnatal care required), and WHO class 4 (pregnancy contraindicated: very high risk of maternal mortality or severe morbidity; termination should be discussed, and if pregnancy continues, care as for class 3) [1]. Recently, five categories of WHO classification were introduced, in which class 2 were divided into two groups with small (class 2) and moderate (class 2-3) increased risk of maternal mortality and morbidity [2].

The second method uses the CARPREG score, which was established based on an investigation of 599 cases of pregnancy with concomitant heart disease. The following five items are regarded as risk factors for maternal complications: (1) New York Heart Association (NYHA) class III–IV, (2) history of cardiovascular events before pregnancy, (3) cyanotic heart disease, (4) stenotic lesion in the left heart, and (5) reduced ventricle function (EF <40%). Each item receives 1 point when present, and the incidence of maternal cardiovascular events during pregnancy is predicted as 0 points = 5%, 1 = 27%, and ≥ 2 = 75% [3]. The incidence of fetal complication was 20%, and the rate of serious complications such as respiration distress syndrome, intracranial hemorrhage, and death was 5%, in addition to premature delivery and low birth weight. The factors aggravating the fetal outcome were NYHA class III or higher or cyanotic heart disease, use of anticoagulants, cigarette smoking, multipara, and stenotic lesion in the left heart [3]. Then the CARPREG II study, which enrolled 1,938 pregnancies and updated the original study, was recently reported. Cardiac complications occured in 16% of pregnancies. In addition to five general predictors, five more predictors were identified; four lesion-speciffic predictors (mechanical valves, high-risk aortopathies, pulmonary hypertension and coronary artery disease) and one clinical care predictor (late pregnancy assessment) [4].

The third method uses the ZAHARA score, which was established from an investigation of 1302 pregnancies with concomitant CHD. The following risk factors are scored: history of arrhythmia, 1.5 points; oral cardiovascular drugs before pregnancy, 1.5; NYHA class ≥II before pregnancy, 0.5; obstructive lesion in the ventricle (pressure gradient (PG) >50 mmHg or aortic valve area (AVA) < 1.0 cm^2), 2.5; moderate or severe atrioventricular valve regurgitation of the ventricle and pulmonary ventricle, 0.75 each; previous mechanical valve replacement, 4.25; and cyanotic heart disease, 1. The incidence of maternal cardiovascular events during pregnancy is predicted based on the total score as ≤0.5 points = 3%; 0.5–1.5 = 8%; 1.5–2.5 = 18%; 2.5–3.5 = 43%; and ≥ 3.5 = 70% [5].

In the Japanese Circulation Society guidelines [6], the following items are specified as heart diseases requiring strict caution during pregnancy or avoidance of pregnancy: (1) pulmonary hypertension (Eisenmenger's syndrome), (2) outflow tract obstruction (severe aortic valvar stenosis mean PG >40–50 mmHg), (3) heart failure (NYHA class III or severer, left ventriclar ejection fraction (LVEF) <35–40%), (4) Marfan syndrome (diastolic aortic diameter >40 mm), (5) mechanical valve, and (6) cyanotic disease (oxygen saturation <85%).

For women who are planning pregnancy, it is preferable to perform counseling as specifically as possible using the above risk assessment methods, reports on outcomes of pregnancy by disease, and experience in the affiliated institution.

Previously, pregnancy risk assessment was performed only for a short period from pregnancy to a specific puerperal period, but the influence of pregnancy and delivery on the long-term outcome of heart disease has recently been reported. This may facilitate counseling, including long-term prognosis, and this approach requires further investigation. Information should also be provided on fetal risks, such as premature delivery, maternal drug therapy, and heredity.

5.2.2 Exercise Tolerance and Pregnancy Risk

Several studies on exercise tolerance and outcomes of pregnancy have been reported. In one Japanese study using the cardiopulmonary exercise testing (CPX) before pregnancy of 33 pregnant women with CHD, maternal cardiovascular events (heart failure and arrhythmia) were likely to occur in cases with maximum heart rate (HR) <150/min and/or peak oxygen consumption (VO_2) <22.0 mL/kg/min, fetal events (premature delivery, underweight, fetal dysfunction, abortion) in cases with maximum HR <150/min and/or peak VO_2 <26.2 mL/kg/min, and obstetric events (post-delivery bleeding, hypertensive disorders in pregnancy, premature abruption of placenta) for maximum HR <150/min and/or peak VO_2 <25.3 mL/kg/min [7]. Maximum HR, percentage of maximum age-predicted HR, and chronotropic index have also been shown to be correlated with maternal and fetal complications in a separate report [8].

5.3 Maternal Cardiovascular Complications

5.3.1 Heart failure

The circulating plasma volume markedly increases in the early to middle phase of pregnancy and averages 1.5 times that in non-pregnancy around the 30th week of gestation. For patients with cardiovascular diseases which are intolerant to volume overload such as pulmonary hypertension, stenotic disease, and severe cardiac dysfunction, attention should be paid to the appearance of heart failure and low cardiac output in the presence of an increased volume load. In delivery, oxygen consumption increases about three times, circulating blood volume increases by 300–500 mL due to uterine contraction with labor pain, and cardiac output increases by 15–25%. The uterus contracts immediately after delivery, which releases the inferior vena cava compressed by the uterus in late pregnancy and rapidly increases venous return. Since the circulating plasma volume is increased during pregnancy, a volume-loaded state transiently occurs after delivery, and its normalization takes about 4–6 weeks. In a study of 173 pregnant women with concomitant heart disease who developed heart failure in the perinatal period, heart failure developed in the 20–30th week in women with structural heart disease, reflecting the increase in circulating plasma volume, whereas heart failure developed at delivery to 1 month after delivery in many women with peripartum cardiomyopathy and ischemic heart disease [9].

5.3.2 Arrhythmia

HR increases by about 20% from that before pregnancy. Since cardiac dilatation (myocardial stretch) accompanies the increase in HR and plasma volume, extrasystole and tachyarrhythmia tend to aggravate during pregnancy. After delivery, sympathetic nerve activity during pregnancy resolves and HR slows, aggravating bradyarrhythmia. In women with long QT syndrome, arrhythmic events more frequently occur during the 9-month period after delivery than before and during pregnancy [10].

5.3.3 Thromboembolism

Coagulation factors increase and are activated during pregnancy, increasing the risk of thrombus and embolus formation. Deep vein thrombosis (DVT) and pulmonary embolism are serious pregnancy-related complications. Coagulability differs with ethnicity. A Japanese study showed that genetic mutations in the protein S gene were predominant in pregnant Japanese DVT women, and DVT in pregnant women with genetic mutations occurred more frequently at the early stage of pregnancy than postpartum [11]. Thrombus formation-induced valve dysfunction and embolism are likely to occur after mechanical valve replacement during pregnancy; careful anticoagulant and antiplatelet therapy is necessary. However, warfarin has a high fetal risk because it is teratogenic and transfers through the placenta, but the use of heparin instead of warfarin increases the risk of maternal thrombosis. Therefore, pregnancy after mechanical valve replacement has a high risk.

5.3.4 Aortic Dissection

During pregnancy, the elastic fiber of the aortic media degenerates due to the influence of estrogen, increasing vulnerability, and the risk of aortic dissection increases in patients with Marfan syndrome, aortitis, and other aortopathies accompanied by aortic dilatation. It has recently been shown that aortic dilatation and dissection occur in patients with CHD, such as tetralogy of Fallot and transposition of the great arteries. Careful course observation is necessary for patients with aortic dilatation.

5.3.5 Infective Endocarditis

The frequency of this disease is not high, but some cases have complication by infective endocarditis caused by obstetric treatment, such as that for delivery. Thus, the Japanese Circulation Society guidelines recommend preventive administration of antimicrobial drugs at delivery to patients at high risk for infective endocarditis [6]. For heart diseases other than high-risk disease, use of antimicrobial drugs is not recommended because the frequency of infective endocarditis is low, but there is a risk-benefit consideration, and administration of these drugs may still be useful for prevention in high-risk patients (see Chap. 7).

5.4 Maternal Long-Term Outcomes After Pregnancy

Pregnancy and delivery may affect long-term outcomes of several diseases and pathologies. In a retrospective study of long-term outcomes of women with Marfan syndrome, previous pregnancy and delivery were significantly correlated with aortic dissection and prophylactic aortic surgery [12]. In a study of pregnancy in patients after a Mustard operation and with transposition of the grate arteries (TGA) in whom the right ventricle was dysfunctional, aggravation of NYHA class (12%), progression of right ventricular (RV) dilatation (31%), RV hypofunction (19%), and an increase in tricuspid regurgitation (29%) were observed long after delivery, suggesting that aggravation remained upon pregnancy [13]. Right cardiac dilatation progresses upon pregnancy and delivery, even in pregnancy after repair of tetralogy of Fallot. In Japanese study, indexes of the left ventricle did not change after pregnancy and delivery, but the RV diameter was significantly dilated 6 months to 1 year after delivery, compared with that before pregnancy [14]. In a study in which RV volume was evaluated by MRI before and after pregnancy after repair of tetralogy of Fallot, RV dilatation had more markedly progressed after delivery in patients in whom it had already progressed before pregnancy [15].

5.5 Fetal Risk

Hereditary risks, risk of premature delivery, and the influence of maternal medication should be mentioned in preconception counseling. CHD is caused by chromosomal aberration, a single gene aberration, environmental factors, or multifactorial inheritance of unknown cause in 8, 2, 5, and 85% of cases, respectively, and the frequency of repeated inheritance of maternal CHD in children is about 3–5% [6]. The accuracy of fetal echography has recently improved, and CHD can be diagnosed in the fetal period in 50–60% of cases. Thus, screening by fetal echography is useful for mothers with CHD. Some diseases are inherited at 50% probability, such as Marfan syndrome and long QT syndrome. Since the risk of premature delivery is high in high-risk pregnancy, explanation of the week of delivery and fetal outcome is necessary. The survival rates of babies born by premature delivery are ≥55%, ≥80%, ≥90%, and ≥95% for births at 22–23, 24–25, 26–27, and 28–29 weeks of gestation, respectively. The main complications are shown in Table 5.1. Counseling on oral drugs taken by the mother is also necessary with regard to effects on the fetus and possible withdrawal or substitution by other drugs.

Table 5.1 Main complications in premature babies

Complications due to immaturity of babies	
By 32nd week	Intraventricular hemorrhage, retinopathy of prematurity
By 34th week	Respiratory distress syndrome
By 36th week	Patent ductus arteriosus, hyperbilirubinemia
Complications due to infection and inflammation	
By 32nd week	Cerebral palsy, sepsis, chronic pulmonary disease, necrotizing enteritis

5.5.1 Weeks of Pregnancy as Time Points in Preconception Counseling

The course of pregnancy should be defined using time points from maternal and fetal perspectives in counseling.

4th–5th week: Pregnancy test kit becomes positive, and withdrawal or switch of drugs is recommended for patients taking teratogenic drugs.

5th week: The fetal sac is confirmed.

6th week: Fetal heartbeats are confirmed.

5th–11th week (period of organogenesis): Exposure to teratogenic factors including drugs increases the fetal deformation risk.

9th–12th week: Some women get dehydrated and/or hypokalemia due to hyperemesis.

About 16th week: Completion of the placenta. Oxygen and nutrients supplied to the fetus become mostly dependent on the placenta.

Before the 22nd week: Extraembryonic survival is impossible, and artificial abortion is possible under the Maternal Protection Law in Japan. For the elective abortion, uterine curettage is performed until the 11th week, and delivery of the embryo by uterine contraction is induced by administration of a prostaglandin preparation after the 12th week. Since blood loss increases with progression of pregnancy, abortion should be performed by the 11th week of pregnancy when possible from the perspective of invasiveness for the mother.

After the 20th week: An increase in blood pressure or blood glucose suggests a diagnosis of hypertensive disorders in pregnancy or gestational diabetes.

22nd—36th week: Delivery in this period is premature, and the risks of fetal death and complications increase at earlier weeks of pregnancy.

37th to before the 42nd week: Full-term delivery.

5.5.2 Preconception Counseling for Women with CHD in Japan

In 2016, Koerten et al. used a questionnaire survey in patients and attending physicians to investigate the status of pregnancy in women with CHD in Germany, Hungary, and Japan [16]. About half of women had a history of pregnancy, and abortion was performed only in 8%, but the abortion rate in high-risk women was about three times higher than that in low-risk women. Less information is available on preconception counseling in Japan.

5.6 Contraception

There is a range of contraceptive methods that can be recommended for use according to the individual's particular circumstances. Among women with severe cardiovascular disease, an unintended pregnancy can lead to significant morbidity and mortality [17]. The incidence of unintended pregnancy among women with congenital heart disease in the United States was nevertheless reported to be as high as

Table 5.2 Efficacy (Pearl Index) and disadvantage in women with cardiovascular disease of typical contraceptive methods

	IUD					
	Copper IUD	LNG-IUS	COC	POP	Male condom	Female sterilization
Pearl Index[a]						
Typical use	0.8	0.2	9		18	0.5
Perfect use	0.6	0.2	0.3		2	0.5
Disadvantage(s)	– Risk of vasovagal reaction and infection at insertion		– Need to be taken at the same time every day		– User dependency	– Usually requires general anesthesia – The psychological effect and risk of regret
			– Thrombogenic potential – Interaction with warfarin metabolism	– Not available in Japan		

IUD intrauterine device, *LNG-IUS* levonorgestrel-releasing intrauterine system, *COC* combined oral contraceptive, *POP* progestogen-only pill

[a]Pearl Index is the index of effectiveness of a birth control method and defined as the number of contraceptive failures per 100 women-years of exposure

54% [18]. For many women with cardiovascular disease, estrogen-containing pills are contraindicated because they are thrombogenic and affect the metabolism of warfarin. Table 5.2 shows efficacy (Pearl Index) and disadvantage in women with cardiovascular disease of typical contraceptive methods. The levonogestrel-releasing intrauterine system (LNG-IUS) has been demonstrated to be effective and safe for contraception in healthy women, and it has been proposed that the LNG-IUS should be a first-line contraceptive method. It may also be effective and safe in women with cardiovascular disease.

References

1. Thorne S, MacGregor A, Nelson-Piercy C (2006) Risks of contraception and pregnancy in heart disease. Heart 92:1520–1525
2. Canobbio MM, Warnes CA, Aboulhosn J et al (2017) Management of pregnancy in patients with complex congenital heart disease: a scientific statement for healthcare professionals from the American Heart Association. Circulation 135:e50–e87
3. Siu SC, Sermer M, Colman JM et al (2001) Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation 104:515–521
4. Silversides CK, Grewal J, Mason J et al (2018) Pregnancy outcomes in women with heart disease: The CARPREG II Study. J Am Coll Cardiol 71(21):2419–2430
5. Drenthen W, Boersma E, Balci A et al (2010) Predictors of pregnancy complications in women with congenital heart disease. Eur Heart J 31:2124–2132
6. JCS Joint Working Group (2011) Guidelines for indication and management of pregnancy and delivery in women with heart disease (JCS 2010): digest version. Circ J 76:240–260
7. Ohuchi H, Tanabe Y, Kamiya C et al (2013) Cardiopulmonary variables during exercise predict pregnancy outcome in women with congenital heart disease. Circ J 77:470–476
8. Lui G, Silversides C, Khairy P et al (2011) Heart rate response during exercise and pregnancy outcome in women with congenital heart disease. Circulation 123:242–248
9. Ruys TP et al (2014) Heart failure in pregnant women with cardiac disease: data from the ROPAC. Heart 100:231–238
10. Seth R et al (2007) Long QT syndrome and pregnancy. J Am Coll Cardiol 49:1092–1098
11. Neki R, Fujita T, Kokame K et al (2011) Genetic analysis of patients with deep vein thrombosis during pregnancy and postpartum. Int J Hematol 94:150–155
12. Donnelly RT, Pinto NM, Kocolas I et al (2012) The immediate and long-term impact of pregnancy on aortic growth rate and mortality in women with Marfan syndrome. J Am Coll Cardiol 60:224–229
13. Guedes A, Mercier LA, Leduc L (2004) Impact of pregnancy on the systemic right ventricle after a Mustard operation for transposition of the great arteries. J Am Coll Cardiol 44:433–437
14. Kamiya C, Iwamiya T, Neki R et al (2012) Outcome of pregnancy and effects on the right heart in women with repaired tetralogy of fallot. Circ J 76:957–963
15. Egidy Assenza G, Cassater D, Landzberg M et al (2013) The effects of pregnancy on right ventricular remodeling in women with repaired tetralogy of Fallot. Int J Cardiol 168:1847–1852
16. Koerten MA, Niwa K, Szatmári A et al (2016) Frequency of miscarriage/stillbirth and terminations of pregnancy among women with congenital heart disease in Germany, Hungary and Japan. Circ J 80:1846–1851
17. Thorne S, Nelson-Piercy C, MacGregor A et al (2006) Pregnancy and contraception in heart disease and pulmonary arterial hypertension. J Fam Plann Reprod Health Care 32:75–81
18. Hinze A, Kutty S, Sayles H et al (2013) Reproductive and contraceptive counseling received by adult women with congenital heart disease: a risk-based analysis. Congenit Heart Dis 8:20–31

Cardiovascular Assessment During Pregnancy

6

Yumi Shiina

Abstract

Appropriate risk stratification for pregnancy in patients with cardiovascular disease is important, and pregnant patients at intermediate and high risk require special care. Physiologic adaptations to the pregnant state occur with peak effects of these changes generally seen late in the second trimester or early in the third trimester. Heart failure and arrhythmia are common major cardiovascular complications, particularly in the second and third trimester and after birth. Even healthy pregnant patients often complain of edema or breathlessness during these periods, so objective cardiovascular assessments are required, particularly for women with heart disease. Imaging investigations in the antenatal and perinatal periods should be performed with minimal risks to the mother and developing fetus. Therefore, noninvasive techniques such as echocardiogram and magnetic resonance imaging that do not use ionizing radiation are preferable. Antenatal and perinatal management by a multidisciplinary team experienced in cardiovascular disease is recommended for women with underlying congenital heart disease and other severe cardiovascular conditions.

Keywords

Echocardiography · Magnetic resonance imaging · Congenital heart disease Multidisciplinary team

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6.1 Care Team and Members During Pregnancy

6.1.1 Where Should Cardiac Assessment and Monitoring Take Place?

Ideally, all pregnant women with heart disease should be referred to a specialist high-risk antenatal service and should have at least one special cardiology review with clinical assessment and transthoracic echocardiogram. The specialist should clarify the anatomical, physiological, and electrical features of the condition and also define the functional status, derive a global risk score for adverse maternal cardiac events in pregnancy, and consider lesion-specific risks. Pregnant patients with cardiac problems can be classified by lesion complexity and graded from simple to highly complex. Table 6.1 shows the modified WHO risk classification of pregnancy with cardiac problems [1], and Table 6.2 focuses on the special team and care, which should be arranged according to level, as follows:

- Level 1—exclusive care with a specialist cardiology review and local obstetric care, with defined lines of communication between specialists [2, 3]
- Level 2—shared care with a regular specialist cardiology review and local obstetric care, with defined lines of communication between specialists
- Level 3—local care with a local cardiology review and local obstetric care, with clearly defined lines of communication between all specialists

Table 6.2 shows an ideal framework for hierarchical care among general physicians, nonspecialist cardiologists, and congenital heart disease (CHD) specialist units.

6.1.2 Sharing Information Among Team Members

A report should be generated that includes diagnosis, a heart diagram, a clinical summary, the anticipated hemodynamic impact of pregnancy, and recent investigations. In the last stages of pregnancy, the report should also provide guidance on delivery planning (monitoring requirements, drugs to be available on the labor ward, requirements for endocarditis prophylaxis, and peri-/postpartum care requirements). There is flexibility in this structure of antenatal clinic provision, in that the care pathway can change and be reassessed if unexpected complications occur or if any of the care providers do not feel comfortable to continue care for any reason. There must also be clear policies outlining the indications for re-referring to the specialist unit. In addition to outpatient review, cases should be discussed in a joint forum (multidisciplinary meeting) once a month. Cardiologists, obstetricians, perinatologists, anesthetists, neonatologists, and others, as part of a multidisciplinary team, should develop a written management plan for labor, delivery, and postnatal

Table 6.1 Modified WHO classification

WHO 1 no risk	WHO 2 if otherwise well and uncomplicated small-risk complications	WHO 2–3 depending on individual	WHO 3 significant risk of complications	WHO 4 contraindication for pregnancy
Uncomplicated, small or mild pulmonary stenosis, ventricular septal defect, patent ductus arteriosus	Unoperated atrial septal defect	Mild left ventricular impairment	Mechanical valve	Pulmonary arterial hypertension of any cause
Mitral valve prolapse with no more than trivial mitral regurgitation	Repaired tetralogy of Fallot	Hypertrophic cardiomyopathy	Systemic right ventricle (e.g., congenitally corrected transposition, simple transposition post-Mustard or Senning repair)	Severe systemic ventricular dysfunction
Successfully repaired simple lesions ostium secundum artrial septal defect, ventricular septal defect, patent ductus arteriosus, total anomalous pulmonary venous drainage	Most arrhythmias	Native or tissue valvular heart disease not considered WHO 4	Post Fontan operation	(NYHA FC III–IV or EF <30%)
Isolated ventricular extrasystoles and atrial ectopic beats		Marfan syndrome without aortic dilatation	Cyanotic heart disease Other complex congenital heart disease	Previous peripartum cardiomyopathy with any residual impairment of left ventricular function Severe left heart obstruction Marfan syndrome with aortic dilated >40 mm

WHO world health organization, *NYHA FC* New York Heart Association functional class, *EF* ejection fraction

Table 6.2 Care levels for pregnant women with heart disease

Level 1 Exclusive care in a specialist unit with a multidisciplinary team	• Repairs of conduits • Fontan • Marfan syndrome • Ebstein anomaly • Pulmonary atresia • Eisenmenger syndrome • Repaired complete transposition of the great arteries (atrial/arterial switch) • Congenitally corrected transposition of the great arteries • Pulmonary hypertension • Cyanotic congenital heart disease • Native coarctation of the aorta • Aortic stenosis • Tetralogy of Fallot with pulmonary regurgitation (moderate) • Ventricular septal defect/aortic regurgitation • Mechanical valves • Hypertrophic cardiomyopathy
Level 2 Shared care between a specialist cardiologist and a local obstetric team	• Repaired coarctation of the aorta • Atrioventricular septal defect • Aortic stenosis • Pulmonary stenosis/pulmonary regurgitation (mild) • Tetralogy of Fallot with minimal residua • Ventricular septal defect/aortic regurgitation
Level 3 Shared care between general adult cardiology unit and a local obstetric team	• Repaired patent ductus arteriosus • Mild pulmonary stenosis • Small ventricular septal defect • Repaired atrial septal defect

care. This care conference is also attended by labor ward midwives, as well as by the core personnel of the high-risk team. The focus is on delivery planning and staff education. The explanation of cardiovascular anatomy and pathophysiology is required in a language that can be understood by competent colleagues not highly trained in cardiology; this is especially relevant for women with CHD, where a schematic diagram of the cardiac anatomy is often helpful for the entire health-care team. The essential factors for successful functioning of a high-risk antenatal care team are good communication and teamwork. “One-stop shopping” (care in the same hospital) can reduce the number of medical visits for pregnant women and enhance immediate communication among doctors in different departments.

6.2 Reliable Risk Scores in Pregnancy with Cardiac Problems

Some studies have suggested that the modified WHO classification (Table 6.1) is more appropriate for all pregnant patients than the CARPREG (Table 6.3) [4] and ZAHARA (Table 6.4) scores [5]. The modified WHO classification is the

Table 6.3 CARPREG risk score

	Point
Prior cardiac event (heart failure, transient ischemic attack, stroke, arrhythmia)	1
NYHA FC III/IV or cyanosis (SPO2 <90%)	1
Left heart obstruction (MVA <2 cm^2, AVA <1.5 cm^2, peak LVOTO >30 mmHg on echocardiogram)	1
Reduced systemic ventricular systolic function (EF <40%)	1

0 point 5%
1 point 27%
>1 point 75%
NYHA FC New York Heart Association functional class, *MVA* mitral valve area, *AVA* aortic valve area, *LVOTO* left ventricular outflow tract obstruction, *EF* ejection fraction

Table 6.4 ZAHARA risk score

	Point
Prior arrhythmia	1.5
NYHA FC III/NYHA FC IV	0.75
Left heart obstruction (AVA <1.0 cm^2, peak LVOTO >50 mmHg)	2.5
Mechanical valve prosthesis	4.25
Systemic atrioventricular valve regurgitation (moderate/severe)	0.75
Pulmonary atrioventricular valve regurgitation (moderate/severe)	0.75
Cardiac medication before pregnancy	1.50
Cyanotic heart disease (corrected and uncorrected)	1.0

NYHA FC New York Heart Association functional class, *AVA* aortic valve area, *LVOTO* left ventricular outflow tract obstruction

only method that takes into account both specific heart lesions (Marfan syndrome, bicuspid aortic valve, tetralogy of Fallot, aortic coarctation, Fontan circulation, or systemic ventricular dysfunction) and general status. This classification and the CARPREG score can be applied to congenital and acquired heart conditions; however, the ZAHARA score is exclusively for women with CHD. The CARPREG score can predict complications in intermediate-risk patients but not in low- and high-risk groups, whereas the ZAHARA score can predict complications in low- and intermediate-risk groups. However, the risk in patients with pulmonary hypertension is underrepresented by these two scores. The better prediction performance of the WHO classification may be attributable to the inclusion of important cardiac lesions or clinical conditions such as systemic right ventricle and pulmonary hypertension, which are relatively uncommon. The disadvantage of the WHO classification is that expert knowledge is sometimes required, especially when choosing the gray zone between WHO II and WHO III. Left ventricular (LV) dysfunction also requires careful interpretation. The CARPREG score includes patients at high risk if LV systolic function is <40%, whereas the WHO classification considers pregnancy to be contraindicated if LVEF is <30% [1]. Overall, a combination of the WHO classification and other risk scores may provide the best assessment of cardiovascular risks in pregnancy [6, 7].

6.3 Cardiac Assessment During Pregnancy

6.3.1 Physiologic Changes and Adaptations

Physiologic adaptations to the pregnant state generally reach peak effects late in the second trimester or early in the third trimester. In particular, a decrease in total peripheral vascular resistance to 40–70% of prepregnancy levels, augmentation of blood volume by 30–50% compared with baseline, an increase in mean heart rate by 10–20 bpm, and ultimately a 30–50% increase in cardiac output can occur [8]. Physiologic anemia results from an increase in plasma volume that exceeds the increase in red blood cell mass. A thorough physical examination is mandatory with consideration of the physiological changes that occur during pregnancy.

6.3.2 Important Items in an Initial Assessment

- Preexisting maternal cardiovascular disease should be addressed before conception, including hypertension, obesity, atherosclerotic disease, heart failure, arrhythmias, thromboembolic events, and CHD (including residual lesions).
- The risk of adverse maternal cardiac, obstetrical, or neonatal events should be evaluated using a combination of general and lesion-specific maternal cardiac risk factors, as well as classic obstetric risk factors.
- If prior to conception, to consider whether a cardiac intervention might improve the eventual outcome of pregnancy may be indicated in the near future independent of pregnancy.
- To ensure that the nature of the condition is well understood by the woman herself.
- To share the risk assessment with the woman and clarify her understanding and tolerance of the identified risks; there is often ambiguity in such assessments, and this should be acknowledged.
- To explore relevant issues of maternal health and life expectancy that might have an impact on the ability to raise and nurture a child.
- To assess the likelihood of recurrence of heart disease in the offspring. When indicated, to consider genetic consultation, genetic testing, and transabdominal fetal echocardiography.
- To be ready to deal with rare occasions when pregnancy has such a high risk that advice against continuation must be offered. Mental support may be required for these women.

6.4 Methods of Cardiac Assessment and Monitoring During Pregnancy

6.4.1 Objective Assessment of Functional Status

Maternal functional class is predictive of a poor outcome during pregnancy and women in NYHA functional class III and class IV, regardless of causes, should be

strongly discouraged from becoming pregnant. Functional status should be assessed objectively and carefully because some women are accustomed to situations as chronic heart failure and low cardiac output or cyanosis and often state that they have no symptoms in their daily lives. Cardiopulmonary tests before pregnancy should be performed if needed. Cardiovascular morbidity is lower, and the live birth rate is higher in mothers in NYHA functional class I compared with others in pregnancies with CHD, and in the CARPREG study, maternal prepregnancy NYHA class >II was an independent predictor of adverse maternal cardiac events during pregnancy [4].

6.4.2 Cardiac Medications in Pregnancy

Cardiac medication should be carefully assessed before conception. The decision to continue medications during pregnancy requires weighing the benefits of use against known or possible risks, which may depend on how many weeks pregnant the patient is.

- Choice of drugs: teratogenic and fetopathic effects of cardiac drugs need to be considered and alternate therapies found when necessary. The risks and benefits of modification of drug therapy have to be addressed in terms of the health and safety of the mother and the fetus; the needs of the two do not always coincide. Such issues arise with many drugs but are particularly problematic for warfarin, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers, amiodarone, and some other antiarrhythmics.
- Anticoagulation: for each patient, the optimal form of therapy must be carefully considered. There is a need for particularly precise control, and dosing requirements change as pregnancy progresses. Drug dosing and frequency may need adjustment in pregnancy because of changes in the volume of distribution of many drugs, increases in glomerular filtration rate enhancing drug excretion, and changes in hepatic metabolism affecting drug processing by the liver.

6.4.3 Family History

Many disorders can be identified by taking a careful personal and family history, including cardiomyopathies, Marfan syndrome, CHD, juvenile sudden death, long QT syndrome, catecholaminergic ventricular tachycardia (VT), and Brugada syndrome. It is important to ask specifically about possible sudden death in the family.

6.4.4 Physical Assessments

Normal findings in a healthy pregnant woman include a mild increase in resting heart rate, widened pulse pressure, peripheral edema, and slight elevation of venous pressure.

- *Heart murmur*
  In the later stages of pregnancy, there is physiological fixed splitting of the second heart sound (S2). Systolic murmurs are common, secondary to increased cardiac output. However, diastolic murmurs are unusual and require further evaluation. When a new pathological murmur is heard, an echocardiogram is indicated.
- *Blood pressure and oxygen saturation*
  It is crucial to measure blood pressure in the left lateral recumbent position using a standardized method and to look for proteinuria, especially with a history or family history of hypertension or preeclampsia. Oximetry should be performed in patients with CHD, particularly cyanotic patients with intracardiac shunts. Cyanosis poses a significant risk to the fetus, with a live birth unlikely or miscarriage (12%) if oxygen saturation is <85% [9]. A patient with bidirectional shunt may become cyanotic in the second or third trimester, secondary to the increased blood volume.

6.4.5 Electrocardiogram (ECG) (Fig. 6.1)

Most pregnant patients have a normal ECG. The ECG changes as a result of the upward shift of the diaphragm caused by the growing uterus. The heart is rotated toward the left, and there is a 15–20 left axis deviation. In the third trimester, Q waves in lead III and aVF and inverted T waves in leads III, V1, and V2 are seen (Fig. 6.1). ECG changes can be related to a gradual change in the position of the heart and may mimic LV hypertrophy and other structural heart diseases. Holter monitoring (24 h tape) should be performed in patients with previous paroxysmal or persistent documented arrhythmia (VT, atrial fibrillation, or atrial flutter) or those with symptoms of palpitations. In a review of 87 pregnancies in 73 women, 44% with normal sinus rhythm at baseline but a history of tachyarrhythmia before pregnancy had a recurrence of tachyarrhythmia [10]. Bradycardia is poorly tolerated in women with underlying cardiac disease, limiting the ability to meet the cardiac output demands of pregnancy, because cardiac output depends on the product of stroke volume and heart rate.

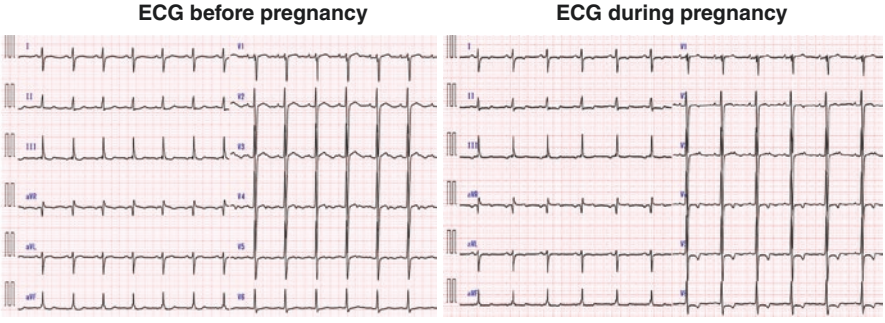

Fig. 6.1 ECG before and during pregnancy

6.4.6 Imaging

- *Chest X-ray* (Fig. 6.2)
  Chest X-ray should be performed as required and without concern about the effect of radiation.
- *Echocardiogram* (Table 6.5)
  An echocardiogram is a noninvasive technique that is very useful for cardiac assessment during pregnancy. Ionizing radiation is not required, allowing simple and repeatable investigations. In a normal pregnancy, a significant increase in cardiac output, LV end-diastolic volume, and LV wall thickness are observed. Depending on the underlying congenital defect, pregnancy can be associated with persistent structural cardiac remodeling, deterioration in valvular dysfunction, and worsening ventricular function. One longitudinal study of cardiac function during pregnancy found permanent reduction in systolic and diastolic LV function, but this issue remains controversial [11].

  The CARPREG risk score is mainly based on women with congenital and valvular heart disease. Significant predictors for an adverse maternal outcome include

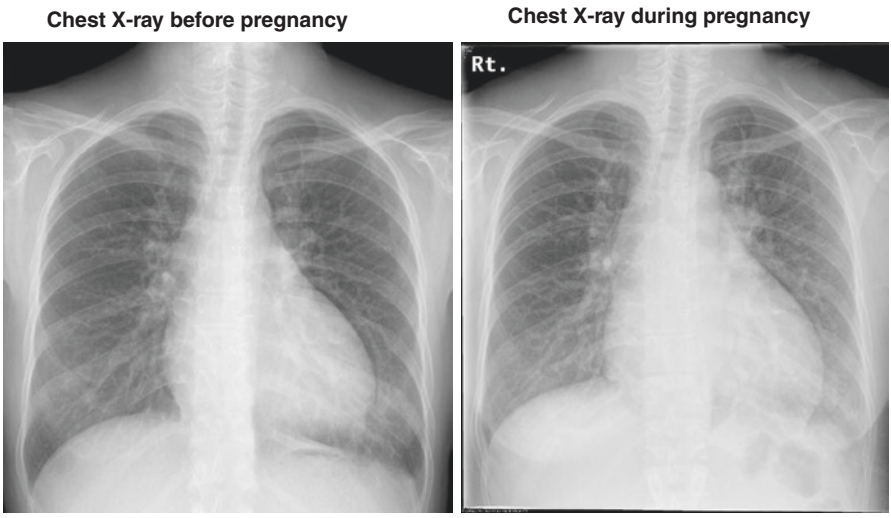

Fig. 6.2 Chest X-ray before and during pregnancy

Table 6.5 Optimal (minimal) timing of echocardiogram

Before pregnancy (baseline)
The peak timing of the cardiac output, late in the second trimester or early in the third trimester
36 weeks pregnancy
4–6 weeks after delivery
In Marfan syndrome, measurements of the aortic root diameter every 4–6 week until 6 months postpartum

left heart obstruction (mitral valve area <2 cm^2, aortic valve area <1.5 cm^2, peak left ventricular outflow tract gradient >30 mmHg by echocardiogram) and reduced systemic ventricular systolic function (ejection fraction <40%). In patients with aortic dilatation, an echocardiogram should be recorded at 6- to 8-week intervals in pregnancy until 6 months postnatally. The subpulmonary ventricle may be vulnerable to the consequences of physiologic volume overload during pregnancy. RV longitudinal systolic function and tricuspid annular plane systolic excursion (TAPSE) are related to impaired uteroplacental circulation and offspring complications [12].

A small study in healthy women showed that the subpulmonary ventricular volume increases far more than the systemic ventricle during pregnancy. This physiological dilatation may be aggravated in women with CHD due to abnormal myoarchitecture, damage from prior surgery, and preexistent volume or pressure overload, leading to persistent subpulmonary ventricle dilatation. For specific congenital lesions including systemic right ventricles and tetralogy of Fallot, pregnancy can be associated with persistent deterioration in cardiac function [13]. Women with cardiovascular complications during pregnancy are at risk for persistent dilatation of the RV; however, the details are unclear, and the relationship between subpulmonary ventricular dilatation and pulmonary valve insufficiency is particularly controversial [14]. Such women are also at higher risk for developing cardiovascular complications and dilatation of the subpulmonary ventricle at 1 year postnatally [15].

- *MRI during pregnancy*
  MRI is increasingly used to evaluate pregnant patients with complex heart disease if an echocardiogram is inconclusive, for example, for a dilated ascending aorta. MRI is considered to be safe from 12 to 18 weeks' gestation [16]. In later gestation, left lateral decubitus positioning may be necessary to prevent caval compression. Clinically, cine MRI and whole heart MRI (MR angiogram) without contrast medium provide enough information in pregnant patients with complex cardiac structure. Pregnancy is a contraindication for gadolinium-containing contrast media to avoid exposing the fetus to drugs and an unknown teratogenic risk. There is no clear evidence that gadolinium agents cause chromosomal damage or are teratogenic for the fetus or neonate after injection in pregnant or breast-feeding mothers, but the potential persistence of gadolinium in amniotic fluid is a concern. Therefore, extra caution during the first trimester may be appropriate.
- *CT during pregnancy: radiation exposure* (Tables 6.6 and 6.7)
  Common cardiovascular complications may occur in 1% of all pregnant women. In such a situation, selection of imaging requires thoughtful planning. The use of radiation, radiopharmaceuticals, and contrast agents should be minimized. Pulmonary and cardiac CT angiography cause minimal fetal radiation exposure and ventilation-perfusion scintigraphy involves relatively low fetal irradiation. Cardiac catheterization, coronary angiography, and electrophysiologic procedures, including complex interventions, also cause relatively low fetal exposure. The effects of radiation on the fetus depend on the dose and the gestational age at which exposure occurs. If possible, procedures should be delayed until at least the end of the period of major organogenesis (12 weeks after menses). There is no evidence of an increased fetal risk of congenital malformations, intellectual disability, growth restriction,

Table 6.6 American College of Radiology relative radiation levels

Adult effective dose estimate range (mSv)	Pediatric effective dose estimate range (mSv)	Example examinations
0	0	Ultrasound, MRI
<0.1	<0.03	Chest radiography, hand radiography
0.1–1	0.03–0.3	Pelvis radiography, mammography
>1–10	>0.3–3	Abdomen CT, nuclear medicine bone scan
>10–30	>3–10	Abdomen CT with and without contrast administration, whole-body PET
>30–100	>10–30	CT angiography chest, abdomen and pelvis contrast administration; transjugular intrahepatic portosystemic shunt placement

Table 6.7 Radiological protection suspected in utero induced deterministic radiation effects

Menstrual or gestational age	Conception age	Radiation dose <50 mGy	Radiation dose 50–100 mGy	Radiation dose >100 mGy
0–2 week		None	None	None
3rd and 4th week	1st to 2nd week	None	Probably none	Possible spontaneous abortion
5th to 10th week	3rd to 8th week	None	Potential effects are scientifically uncertain and probably too subtle to be clinically detectable	Possible malformations increasing in likelihood as dose increases
11th to 17th week	9th to 15th week	None	Potential effects are scientifically uncertain and probably too subtle to be clinically detectable	Increased risk of deficits in intelligence quotient or mental retardation that increase in frequency and severity with increasing dose
18th to 27th week	16th to 25th week	None	None	Intelligence quotient deficits not detectable at diagnostic doses
>27 week	>25 week	None	None	None applicable to diagnostic medicine

or pregnancy loss at radiation doses to the pregnant woman of 50 mGy [17–21]. There may be a small increase in risk (1:2000 vs. 1:3000) of childhood cancer [17–21]. Some evidence suggests that risk of malformations is increased at high doses, whereas the risk at doses of 50 to 100 mGy is less clear. In the first 14 days after fertilization, intact survival without fetal abnormality or death is the most likely an outcome of radiation exposure of 50 mGy. After the first 14 days, radiation of 50 mGy may be associated with an increased risk of congenital malformations, growth restriction, and intellectual disability. Most medical procedures do not expose the fetus to such high levels of radiation (Table 6.7). For most diagnostic medical

procedures involving doses to the fetus of up to 1 mGy, the associated risks of childhood cancer are very low. Shielding of the maternal abdomen (fetus) is required, but is not completely effective because of radiation scattering.

6.4.7 Laboratory

- *BNP and NT-pro-BNP*
  Increased B-type natriuretic peptide (BNP) levels are found during pregnancy in many women with heart disease. BNP <100 pg/mL has a negative predictive value of 100% for identifying events during pregnancy [22]. Therefore, evaluating serial BNP levels during pregnancy could be helpful to exclude suspected adverse cardiac events. In the ZAHARA II study, the negative predictive value of NT-pro-BNP <128 μg/mL at 20 weeks of gestation was 96.9% [23]. Increased NT-pro-BNP at 20 weeks of gestation is an independent predictor of cardiovascular events in women with CHD. Women with cardiovascular events in pregnancy have significantly higher NT-pro-BNP at 1 year postnatally compared to women without cardiovascular events in pregnancy, and NT-pro-BNP <128 μg/mL at 20 weeks of gestation has a negative predictive value of 98.7% for occurrence of cardiovascular events 1 year postnatally [15].
- *CK and troponin*
  For the diagnosis of acute coronary syndrome (ACS), creatine kinase (CK), CKMB, and troponin may be useful, but careful interpretation is required. During labor, elevated CK occurs due to uterine contractions, and these levels normalize during the second day after labor. Troponin T or troponin I is not elevated in normal pregnancy but can be elevated in patients with preeclampsia or a hypertensive crisis [24].
- *D-dimer and ultrasonography in deep venous thrombosis* (*DVT*) (Table 6.8)

Table 6.8 Radiation exposure of various imaging examinations performed for pulmonary embolism

Examination	Effective whole-body dose (mSv)	Fetal dose (mGy)	Effective dose per breast (mGy)
Posteroanterior or lateral chest radiography	0.06–0.25	0.01	
Low-dose perfusion scintigraphy	0.6–1.0	0.1–0.37	0.11–0.3
Ventilation-perfusion scintigraphy	1.2–6.8	0.1–0.8	0.22–0.28
Low-dose pulmonary CT angiography	2–20	0.01–0.66	10–70
Pulmonary digital subtraction angiography	2.7		
Pulmonary digital subtraction angiography	3.2–30.1	0.5	
Evaluation of background radiation	2.5	1.1–2.5	

D-dimer levels increase physiologically with each trimester. In one study, the mean preconception of D-dimer concentration of 0.43 mg/L increased in the first, second, and third trimesters to 0.58, 0.83, and 1.16, respectively, indicating a 39% increase in D-dimer for each trimester compared with the previous one [25]. Thus, a positive D-dimer test based on the conventional cutoff level is not necessarily indicative of DVT, and new cutoff levels are needed based on further objective testing.

Compression ultrasound is the diagnostic imaging procedure of choice for suspected DVT in pregnancy. This method has high sensitivity and specificity for proximal DVT but less for distal DVT and DVT in the vasculature of the pelvis. Serial compression ultrasound evaluations in pregnancy give a high negative predictive value of 99.5% [25]. If a proximal DVT is detected, treatment should be continued. Ideally, women with suspected DVT in pregnancy should be assessed for pretest probability and then undergo a D-dimer test and compression ultrasonography. In a case with a high pretest probability, a positive D-dimer test, and normal initial compression, magnetic resonance venography may be used to exclude isolated pelvic DVT.

6.5 Postnatal Follow-Up

We provide a postnatal cardiac review at the same time as the obstetric postnatal check, typically at 4–6 weeks after birth. Little is known about the long-term effects of pregnancy on maternal cardiac status, but there is the evidence in normal women that pregnancy-related physiological changes resolve by 6 months after delivery.

References

1. Thorne S, MacGregor A, Nelson-Piercy C (2006) Risks of contraception and pregnancy in heart disease. Heart 92(10):1520–1525
2. Deanfield J, Thaulow E, Warnes C, Webb G, Kolbel F, Hoffman A, Sorenson K, Kaemmer H, Thilen U, Bink-Boelkens M, Iserin L, Daliento L, Silove E, Redington A, Vouhe P, Priori S, Alonso MA, Blanc JJ, Budaj A, Cowie M, Deckers J, Fernandez Burgos E, Lekakis J, Lindahl B, Mazzotta G, Morais J, Oto A, Smiseth O, Trappe HJ, Klein W, Blömstrom-Lundqvist C, de Backer G, Hradec J, Mazzotta G, Parkhomenko A, Presbitero P, Torbicki A, Task Force on the Management of Grown Up Congenital Heart Disease, European Society of Cardiology; ESC Committee for Practice Guidelines (2003) Management of grown up congenital heart disease. Eur Heart J 24(11):1035–1084
3. Connelly MS, Webb GD, Somerville J, Warnes CA, Perloff JK, Liberthson RR, Puga FJ, Collins-Nakai RL, Williams WG, Mercier LA, Huckell VF, Finley JP, McKay R (1998) Can J Cardiol 14(3):395–452
4. Siu SC, Sermer M, Harrison DA, Grigoriadis E, Liu G, Sorensen S, Smallhorn JF, Farine D, Amankwah KS, Spears JC, Colman JM (1997) Risk and predictors for pregnancy-related complications in women with heart disease. Circulation 96(9):2789–2794
5. Drenthen W, Boersma E, Balci A, Moons P, Roos-Hesselink JW, Mulder BJ, Vliegen HW, van Dijk AP, Voors AA, Yap SC, van Veldhuisen DJ, Pieper PG, ZAHARA Investigators (2010) Predictors of pregnancy complications in women with congenital heart disease. Eur Heart J 31(17):2124–2132

6. CW L, Shih JC, Chen SY, Chiu HH, Wang JK, Chen CA, Chiu SN, Lin MT, Lee CN, Wu MH (2015) Comparison of 3 risk estimation methods for predicting cardiac outcomes in pregnant women with congenital heart disease. Circ J 79(7):1609–1617
7. Balci A, Sollie-Szarynska KM, van der Bijl AG, Ruys TP, Mulder BJ, Roos-Hesselink JW, van Dijk AP, Wajon EM, Vliegen HW, Drenthen W, Hillege HL, Aarnoudse JG, van Veldhuisen DJ, Pieper PG, ZAHARA-II Investigators (2014) Prospective validation and assessment of cardiovascular and offspring risk models for pregnant women with congenital heart disease. Heart 100(17):1373–1381
8. Hebson C, Saraf A, Book WM (2016) Risk assessment and Management of the Mother with cardiovascular disease. Clin Perinatol 43:1):1–1)22
9. Presbitero P, Somerville J, Stone S, Aruta E, Spiegelhalter D, Rabajoli F (1994) Pregnancy in cyanotic congenital heart disease. Outcome of mother and fetus. Circulation 89(6):2673–2676
10. Silversides CK, Harris L, Haberer K, Sermer M, Colman JM, Siu SC (2006) Recurrence rates of arrhythmias during pregnancy in women with previous tachyarrhythmia and impact on fetal and neonatal outcomes. Am J Cardiol 97(8):1206–1212
11. Kampman MA, Valente MA, van Melle JP, Balci A, Roos-Hesselink JW, Mulder BJ, van Dijk AP, Oudijk MA, Jongbloed MR, van Veldhuisen DJ, Pieper PG, ZAHARA II Investigators (2016) Cardiac adaption during pregnancy in women with congenital heart disease and healthy women. Heart 102(16):1302–1308
12. Pieper PG, Balci A, Aarnoudse JG, Kampman MA, Sollie KM, Groen H, Mulder BJ, Oudijk MA, Roos-Hesselink JW, Cornette J, van Dijk AP, Spaanderman ME, Drenthen W, van Veldhuisen DJ, ZAHARA II Investigators (2013) Uteroplacental blood flow, cardiac function, and pregnancy outcome in women with congenital heart disease. Circulation 128(23):2478–2487
13. Uebing A, Arvanitis P, Li W, Diller GP, Babu-Narayan SV, Okonko D, Koltsida E, Papadopoulos M, Johnson MR, Lupton MG, Yentis SM, Steer PJ, Gatzoulis MA (2010) Effect of pregnancy on clinical status and ventricular function in women with heart disease. Int J Cardiol 139(1):50–59
14. Egidy Assenza G, Cassater D, Landzberg M, Geva T, Schreier J, Graham D, Volpe M, Barker N, Economy K, Valente AM (2013) The effects of pregnancy on right ventricular remodeling in women with repaired tetralogy of Fallot. Int J Cardiol 168(3):1847–1852
15. Kampman MA, Balci A, Groen H, van Dijk AP, Roos-Hesselink JW, van Melle JP, Sollie-Szarynska KM, Wajon EM, Mulder BJ, van Veldhuisen DJ, Pieper PG, ZAHARA II Investigators (2015) Cardiac function and cardiac events 1-year postpartum in women with congenital heart disease. Am Heart J 169(2):298–304
16. Bulas D, Egloff A (2013) Benefits and risks of MRI in pregnancy. Semin Perinatol 37(5):301–304
17. ACOG Committee on Obstetric Practice (2004) ACOG Committee opinion number 299, September 2004 (replaces no. 158, September 1995): guidelines for diagnostic imaging during pregnancy. Obstet Gynecol 104:647–651
18. Chintapalli KN, Montgomery RS, Hatab M, Katabathina VS, Guiy K (2012) Radiation dose management: part 1, minimizing radiation dose in CT-guided procedures. AJR Am J Roentgenol 198(4):W347–W351
19. Goldberg-Stein SA, Liu B, Hahn PF, Lee SI (2012) Radiation dose management: part 2, estimating fetal radiation risk from CT during pregnancy. AJR Am J Roentgenol 198(4):W352–W356
20. Wang PI, Chong ST, Kielar AZ, Kelly AM, Knoepp UD, Mazza MB, Goodsitt MM (2012) Review. Imaging of pregnant and lactating patients: part 1, evidence-based review and recommendations. Am J Roentgenol 198:778–784
21. Wang PI, Chong ST, Kielar AZ, Kelly AM, Knoepp UD, Mazza MB, Goodsitt MM (2012) Review. Imaging of pregnant and lactating patients: part 2, evidence-based review and recommendations. Am J Roentgenol 198:785–792
22. Tanous D, Siu SC, Mason J, Greutmann M, Wald RM, Parker JD, Sermer M, Colman JM, Silversides CK (2010) B-type natriuretic peptide in pregnant women with heart disease. J Am Coll Cardiol 56(15):1247–1253

23. Kampman MA, Balci A, van Veldhuisen DJ, van Dijk AP, Roos-Hesselink JW, Sollie-Szarynska KM, Ludwig-Ruitenberg M, van Melle JP, Mulder BJ, Pieper PG, ZAHARA II Investigators (2014) N-terminal pro-B-type natriuretic peptide predicts cardiovascular complications in pregnant women with congenital heart disease. Eur Heart J 35(11):708–715
24. Bozkurt M, Yumru AE, Sahin L, Salman S (2015) Troponin I and D-dimer levels in preeclampsia and eclampsia: prospective study. Clin Exp Obstet Gynecol 42(1):26–31
25. Simcox LE, Ormesher L, Tower C, Greer IA (2015) Pulmonary thromboembolism in pregnancy: diagnosis and management. Breathe (Sheff) 11(4):282–289

Infective Endocarditis

7

Satoshi Nakatani

Abstract

Infective endocarditis can be life-threatening unless early diagnosis is made and effective therapy is started. Although the incidence of infective endocarditis is low in pregnancy, maternal and fetal mortality is high once occurred. Therefore, any pregnant woman with unexplained fever and a heart murmur should be observed carefully. There is still a controversy about preventive administration of antibiotics during pregnancy. However, considering poor outcome of pregnant woman with infective endocarditis, it may be reasonable to use antibiotics in patients at high risk.

Keywords

Endocarditis · Infection · Echocardiography · Congenital heart disease · Antibiotics

7.1 Overview

Infective endocarditis is a serious septic disease which can be life-threatening unless effective therapy under correct diagnosis is made. It is considered to be mostly based on non-bacterial thrombotic endocarditis caused by high or turbulent flow inside the heart or vessels and bacteremia. Bacteremia may develop after spontaneous abortion, vaginal delivery assisted by episiotomy or cesarean section, and due to urogenital infection and indwelling catheters. Thus, a pregnant woman with a heart disease can develop infective endocarditis because she has a possibility of both turbulent intracardiac flow and bacteremia. However, the

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incidence of infective endocarditis during pregnancy is very low. The incidence was reported to be 1:8000 pregnancies 35 years ago [1]. A similar incidence, 0.006%, has been shown in the guidelines from the European Society of Cardiology [2]. According to a more recent search of peer-reviewed literature published between 1985 and 2006, the rate of endocarditis was 0.5% during 1372 completed pregnancies among women with congenital heart disease [3]. In one systematic review covering the literatures between 1965 and 2002, there were 68 cases with infective endocarditis complicating pregnancy [4]. Eighteen cases (27%) occurred postpartum, and underlying heart disease was noted in 21 cases (31%). Intravenous drug use was found in three cases (4.4%) and recent dental work five cases (7.4%). The overall maternal and fetal mortality rates were 22.1% and 14.7%, respectively. The valve-specific maternal mortality was 42.1% (8/19), 21.7% (5/23), and 9.5% (2/21) for aortic, mitral, and tricuspid valves, respectively. The other report showed even higher maternal mortality (33%) and fetal mortality (29%) [5]. Despite the high maternal and fetal mortality, urgent surgery should be performed during pregnancy in women who present with heart failure due to acute regurgitation. Rapid detection of infective endocarditis and appropriate treatment are important in reducing the risk of both maternal and fetal mortality [5]. Thus, any pregnant woman with unexplained fever and a heart murmur should be observed carefully.

7.2 Diagnosis

Almost all patients have a heart murmur, and infective endocarditis should be suspected in any such patients with unexplained fever. Sometimes, embolism may be the first feature to visit physicians. Although heart failure is often seen in patients with newly occurred or worsening valvular regurgitation, it is challenging to diagnose infective endocarditis because of the changing cardiovascular physiology during pregnancy.

Diagnosis of infective endocarditis has been usually made according to the modified Duke criteria (Table 7.1) [6]. It is based on clinical, microbiological, and echocardiographic findings, and the major criteria are mainly focused on microbiological culture and positive endocardial involvement, as assessed by echocardiography either initially transthoracic echocardiography or subsequently the more sensitive transesophageal echocardiography. Recent guidelines from the European Society of Cardiology on infective endocarditis have advocated the use of other imaging modalities other than echocardiography such as multi-slice computed tomography (CT), magnetic resonance imaging, and nuclear imaging [2]. Several reports have shown promising results for ^{18}F-FDG-PET/CT imaging in prosthetic valve endocarditis [7]. Thus, when the conventional diagnostic approaches are inconclusive, yet there is a strong clinical suspicion of infective endocarditis, it is important to acknowledge that ^{18}F-FDG-PET/CT approach may play in aiding the diagnosis and management of the complicated cases.

Table 7.1 Definition of terms used in the proposed modified Duke criteria for the diagnosis of infective endocarditis (IE) [6]

Major criteria
Blood culture positive for IE
Typical microorganisms consistent with IE from two separate blood cultures:
Viridans streptococci, *Streptococcus bovis, HACEK* group, *Staphylococcus aureus*
Community-acquired enterococci, in the absence of a primary focus
Microorganisms consistent with IE from persistently positive blood cultures, defined as follows:
At least two positive cultures of blood samples drawn >12 h apart
All of three or a majority of ≥4 separate cultures of blood (with first and last sample drawn at least 1 h apart)
Single positive blood culture for Coxiella burnetii or antiphase I IgG antibody titer >1:800
Evidence of endocardial involvement
Echocardiogram positive for IE (TEE recommended in patients with prosthetic valves, rated at least "possible IE" by clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in other patients), defined as follows:
Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets
On implanted material in the absence of an alternative anatomic explanation
Abscess
New partial dehiscence of prosthetic valve
New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)
Minor criteria
Predisposition, predisposing heart condition, or injection drug use
Fever, temperature >38 °C
Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions
Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor
Microbiological evidence: positive blood culture but does not meet a major criterion as noted above[a]
Serological evidence of active infection with organism consistent with IE

TEE transesophageal echocardiography, *TTE* transthoracic echocardiography
[a]Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis

7.3 Underlying Disease

Since non-bacterial thrombotic endocarditis is considered to relate closely to the occurrence of infective endocarditis, some heart diseases are regarded as being at high risk. They include patients with previous infective endocarditis, unrepaired cyanotic congenital heart disease, and completely repaired congenital heart defect with prosthetic material or device.

We performed the multicenter registry for patients with infective endocarditis [8]. There were 513 cases with infective endocarditis from 2007 to 2009. Among them, underlying cardiac disease was found in 353 (69%), and the majority had valvular heart disease (287 cases). The leading valvular heart disease was mitral regurgitation (145 cases), and the second leading one was aortic regurgitation (76 cases). Mitral valve prolapse was involved in 55 cases, and bicuspid aortic valve was involved in 24 cases. Congenital heart disease was found in 23 cases, and there were 18 cases with ventricular septal defect. This was a nationwide survey of infective endocarditis, and there was no description on a pregnant woman with infective endocarditis. In the previously mentioned review of 68 cases, mitral valve was damaged in 23 cases, and aortic valve was damaged in 19 cases [4]. Although no data have been available of underlying heart diseases for infective endocarditis during pregnancy, mitral regurgitation and aortic regurgitation with or without congenital heart disease may have to be carefully observed.

7.4 Predisposing Factors

Again, there has been no data on predisposing factors in pregnant women, but the data from general population could serve as a useful reference. In the nationwide survey in Japan described above [8], about 60% had some predisposing factors. The major factor was decayed teeth or periodontitis accounting 40% of those with predisposing factors. Notably, infective endocarditis occurred without any predisposing factors in about 40% of all patients.

Apparent routes for infection were not identified in about 60% of all patients. Among 196 cases with identified routes, 81 claimed occurrence of infective endocarditis after dental treatment including cavity treatment ($n = 61$), dental extraction ($n = 13$), and scaling ($n = 5$). Intravenous drug injection could be related to the occurrence in 15 cases.

7.5 Causative Organisms

Organisms cultured from the vagina and postpartum uterus have been reported to cause infective endocarditis after obstetric and gynecological procedures [9]. However, any organism capable of causing infective endocarditis may cause it in pregnancy. The range of organisms is thus probably similar to infective endocarditis in the general population. According to a systematic review of 90 cases obtained from 72 studies published during 1988 and 2012, the most common organisms were streptococcal (43%) and staphylococcal (26%) species in infective endocarditis complicated with pregnancy [10]. In our previous registry of infective endocarditis in general population, streptococci were found in approximately 50%, and staphylococci were found in 30%. Methicillin-resistant *Staphylococcus aureus* (MRSA) was found in 7.5% [8]. The organisms could be influenced by periods and regions. It has been recognized that prevalence of MRSA has been increasing in western

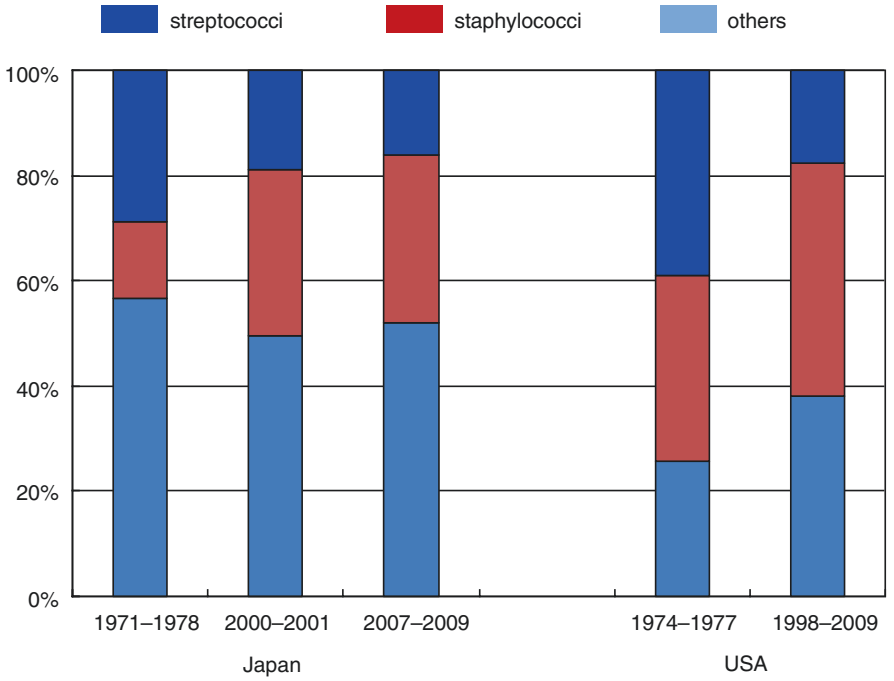

Fig. 7.1 Prevalence of streptococci, staphylococci, and others in Japan and the USA. Prevalence of staphylococci has been increasing recently in Japan. However, it is still less than that in the USA

countries but not so much in Japan [11]. Figure 7.1 shows the changes in the spectrum of causative organisms in Japan [8, 12, 13] and the USA [14, 15]. In Japan, streptococci are more common than staphylococci, but the prevalence of staphylococci seems to be increasing. In the USA, staphylococci were more common than streptococci 40 years ago and also in today.

7.6 Prophylaxis

In the most recent guidelines from the European Society of Cardiology [2], antibiotic prophylaxis should be restricted to patients with highest risks (patients with the highest incidence of infective endocarditis and/or highest risk of adverse outcome from infective endocarditis). Table 7.2 shows cardiac conditions at highest risk of infective endocarditis for which prophylaxis should be considered when a high-risk procedure is performed [2]. The American Heart Association/American College of Cardiology guidelines for infective endocarditis have also proposed the similar recommendations about antibiotic prophylaxis [16]. According to the European Society of Cardiology guidelines, prophylactic use of antibiotics in the highest-risk patients for vaginal and cesarean delivery is class III because there is no strong evidence that bacteremia causing infective endocarditis results from such procedures [2]. On the

Table 7.2 Cardiac conditions at highest risk of infective endocarditis for which prophylaxis should be considered when a high-risk procedure is performed [2]

Recommendations	Class[a]	Level[b]
Antibiotic prophylaxis should be considered for patients at highest risk for IE: (1) Patients with any prosthetic valve, including a transcatheter valve, or those in whom any prosthetic material was used for cardiac valve repair (2) Patients with a previous episode of IE (3) Patients with CHD: (a) Any type of cyanotic CHD (b) Any type of CHD repaired with a prosthetic material, whether placed surgically or by percutaneous techniques, up to 6 months after the procedure or lifelong if residual shunt or valvular regurgitation remains	IIa	C
Antibiotic prophylaxis is not recommended in other forms of valvular or CHD	III	C

CHD congenital heart disease, *IE* infective endocarditis
[a]Class of recommendation
[b]Level of evidence

other hand, in the American Heart Association/American College of Cardiology guidelines for the management of adults with congenital heart disease, it is reasonable to consider antibiotic prophylaxis against infective endocarditis before vaginal delivery at the time of membrane rupture in selected patients with the highest risk of adverse outcomes [17].

The Japanese Circulation Society guidelines for the prevention and treatment of infective endocarditis recommend that the prevention of infective endocarditis be considered for most patients with congenital heart diseases [18]. Antibiotic treatment of infective endocarditis should be performed for pregnant patients in a fashion similar to that for nonpregnant patients. The patients with a high risk for infective endocarditis who should be recommended to receive prophylactic antibiotics during obstetric operations/procedures and delivery include (1) patients with a history of infective endocarditis; (2) patients with congenital heart disease including those with cyanotic heart disease, those who underwent complete repair using artificial patches and devices within 6 months, and those who underwent repair and have remaining shunts around the implanted artificial patches and devices; (3) patients using artificial valves; and (4) patients after heart transplant (receiving immunosuppressants or having valvular heart disease) [19] In contrast, it is not recommended for patients in whom the risk for infective endocarditis is not high because of its low incidence. However, the benefits of preventive antimicrobial treatment are not denied considering the risk-benefit balance. Currently, there are no guidelines available for the preventive administration of antimicrobial agents during delivery. Considering that the most common causative organism of infective endocarditis in urogenital or gastrointestinal surgeries or procedures is *Enterococcus faecalis*, it may be reasonable to use antibiotics such as ampicillin, gentamicin, and vancomycin in patients at high risk as shown in the Japanese Circulation Society guidelines [19].

References

1. Ward H, Hickman RC (1971) Bacterial endocarditis in pregnancy. Aust N Z J Obstet Gynaecol 11:189–191
2. Habib G, Lancellotti P, Manuel J, Antunes MJ et al (2015) 2015 ESC guidelines for the management of infective endocarditis. Eur Heart J 36:3075–3123
3. Drenthen W, Pieper PG, Roos-Hesselink JW, van Lottum WA, Voors AA, Mulder BJ, van Dijk AP, Vliegen HW, Yap SC, Moons P, Ebels T, van Veldhuisen DJ, ZAHARA Investigators (2007) Outcome of pregnancy in women with congenital heart disease: a literature review. J Am Coll Cardiol 49:2303–2311
4. Campuzano K, Roqué H, Bolnick A, Leo MV, Campbell WA (2003) Bacterial endocarditis complicating pregnancy: case report and systematic review of the literature. Arch Gynecol Obstet 268:251–255
5. Dajani AS, Taubert KA, Wilson W et al (1997) Prevention of bacterial endocarditis. Recommendations by the American Heart Association. Circulation 96:358–366
6. Li JS, Sexton DJ, Mick N et al (2000) Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 30:633–638
7. Saby L, Laas O, Habib G et al (2013) Positron emission tomography/computed tomography for diagnosis of prosthetic valve endocarditis: increased valvular 18F-fluorodeoxyglucose uptake as a novel major criterion. J Am Coll Cardiol 61:2374–2382
8. Nakatani S, Mitsutake K, Ohara T et al (2013) Recent picture of infective endocarditis in Japan. Lessons from cardiac disease registration (CADRE-IE). Circ J 77:1558–1564
9. Lein JN, Stander RW (1959) Subacute bacterial endocarditis following obstetric and gynecologic procedures. Obstet Gynecol 13:568–573
10. Kebed KY, Bishu K, Al Adham RI et al (2014) Pregnancy and postpartum infective endocarditis: a systematic review. Mayo Clin Proc 89:1143–1152
11. Iwakura K (2013) Current profile of infective endocarditis in Japan. Circ J 77:1411–1413
12. Katsu M (1980) Present situation around infective endocarditis. J Jpn Med Assoc 84:869–886
13. Nakatani S, Mitsutake K, Hozumi T et al (2003) Current characteristics of infective endocarditis in Japan: an analysis of 848 cases in 2000 and 2001. Circ J 67:901–905
14. Mylonakis E, Calderwood SB (2001) Infective endocarditis in adults. N Engl J Med 345:1318–1330
15. Bor D, Woolhandler S, Nardin R, Brusch J, Himmelstein D (2013) Infective endocarditis in the U.S., 1998–2009: a nationwide study. PLoS One 8:10
16. Nishimura RA, Carabello BA, Faxon DP et al (2008) ACC/AHA 2008 guideline update on valvular heart disease: focused update on infective endocarditis: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. Circulation 118:887–896
17. Warnes CA, Williams RG, Bashore TM et al (2008) ACC/AHA 2008 guidelines for the management of adults with congenital heart disease. Circulation 118:e714–e833
18. Guidelines for the prevention and treatment of infective endocarditis (JCS 2008). http://www.jcirc.or.jp/guideline/pdf/JCS2017_nakatani_h.pdf (available in March 2018) (in Japanese)
19. JCS Joint Working Group (2012) Guidelines for indication and management of pregnancy and delivery in women with heart disease (JCS 2010). Digest version. Circ J 76:240–260

Maternal Death in Japan

8

Kazuhiro Osato

Abstract

Maternal death in Japan decreased dramatically over these 2 decades. Although the most prevalent cause of maternal death has still been obstetrical bleeding, the relative number of its cases decreased, while the relative number of deaths from cardiovascular disease increased. The causes of maternal death were aortic dissection, peripartum cardiomyopathy, sudden cardiac arrest, and pulmonary hypertension.

Keywords

Maternal death · Obstetrical bleeding · Peripartum cardiomyopathy · Sudden cardiac arrest · Pulmonary hypertension

8.1 Definition of Maternal Death

World Health Organization (WHO)'s International Classification of Diseases (ICD)-MM defined "maternal death" as the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and the site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes [1].

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8.2 Maternal Death in the World

WHO conducted a study on the maternal death, and they estimated that there were 342,900 (uncertainty interval 302,100–394,300) maternal deaths worldwide in 2008, down from 526,300 (446,400–629,600) in 1980 [2]. They also found huge geographical differences. More than 50% of all maternal deaths were in only six countries in 2008 (India, Nigeria, Pakistan, Afghanistan, Ethiopia, and the Democratic Republic of the Congo). The most frequent cause of maternal deaths was also different between regions [3]. Hemorrhage was the leading cause of deaths in Africa (33.9%) and in Asia (30.8%). In Latin America and the Caribbean, hypertensive disorders were responsible for the most deaths (25.7%). Abortion deaths were the highest in Latin America and the Caribbean (12%), which can be as high as 30% of all deaths in some countries in this region. Deaths due to sepsis were higher in Africa (odds ratio 2.71), Asia (1.91), Latin America, and the Caribbean (2.06) than in developed countries.

8.2.1 Maternal Death in Developed Countries

As mentioned above, maternal mortality ratio and frequent causes of maternal deaths are far different between regions and economic conditions of each country.

8.2.1.1 Maternal Death in the United States

Hemorrhage was the leading cause of maternal mortality in the United States during 1987–1990. Thrombotic pulmonary embolism, hypertensive disorder of pregnancy, and infection were also prevalent causes of maternal mortality during the same period. While deaths from those etiologies have been decreasing, the deaths from cardiovascular disease (CVD), such as cardiomyopathy, cardiovascular accident, and other cardiovascular conditions, have been increasing. Deaths from CVD have become the most prominent cause of maternal death in the United States [4].

8.2.1.2 Maternal Death in the United Kingdom

The United Kingdom (UK) Confidential Enquiry into Maternal Deaths, the oldest and the most detailed investigation system in the world, reported in the MBRRACE-UK Maternal Report in 2016 [5] that 23% of maternal mortality was caused by cardiac conditions, which were the leading cause of maternal death. The report gave the key messages at the top of the article: 8.5 per 100,000 died during pregnancy or up to 6 weeks after the ending of pregnancy between 2012 and 2014, and 2 women per 100,000 died from CVD. Thus, cardiac disease is the most frequent cause in the United Kingdom, as in the United States. Women known to have a heart disease are at high risk and need specialist care. Moreover, some women without prior history of CVD died from sudden arrhythmias, myocardial infarction, aortic dissection, and heart failure. Pregnant women should be aware of severe chest pain spreading to the left arm or back that may be cardiac: Persistent breathlessness, when lying, is not normal in pregnancy and may mean heart problems.

8.3 Maternal Death in Japan

As seen by causes of maternal death, there are some differences between the two countries mentioned above and Japan. Japan Association of Obstetricians and Gynecologists (JAOG) and the research group for maternal death established a maternal death enquiry system in 2010. In the detailed reports from the research group, a substantial increase in death from CVD was observed, as seen in other developed countries.

8.3.1 The Confidential Inquiry into Maternal Deaths Research Group (CIMDRG)

Toward the goal of reducing the rate of maternal deaths in Japan, the Confidential Inquiry into Maternal Deaths Research Group (CIMDRG) was created in 1995 [6]. The CIMDRG did a 2-year investigation on maternal death in Japan from 1991 to 1992. Since then, no research concerning maternal mortality has been done, and information about maternal death in the most recent 20 years could only be obtained through death certification data collected and processed by the Statistics and Information Department, Ministry of Health and Welfare. The CIMDRG was reintroduced in 2010, and it reestablished a data collection system collaborating with the JAOG, to which most of the obstetricians and gynecologists in Japan belong [7].

8.3.2 Causes of Maternal Death in Japan

Analysis of the data of the CIMDRG from 2010 to 2015 (266 cases) revealed that the leading cause was obstetrical bleeding (23%), followed by intracranial hemorrhage (16%), amniotic fluid embolism (13%), CVD (9%), infection (7%), and pulmonary embolism (6%) (CIMDRG data, Fig. 8.1). As for the deaths from CVD, prevalence of the death from cardiomyopathy and cerebral and cardiovascular reasons in all maternal death increased significantly, compared to the former CIMDRG data, despite maternal death from other causes significantly having decreased. Figure 8.2 depicts maternal mortality rate per 100,000 for the two periods: 1991–1992 and 2010–2012. Mortality associated with CVD increased from 0.28 to 0.46 (per 100,000) [8].

8.3.3 Cardiovascular Disease and Maternal Death in Japan

A total of 154 maternal deaths were reported in Japan from January 2010 to December 2012. Fifteen women (9.7%) died of CVD [8]. Among all cases of maternal death, only five women (8%) died due to obstetric causes occurring in more than 42 days, but less than 12 months, after the end of pregnancy. In two such late maternal death cases, the cause of death was CVD.

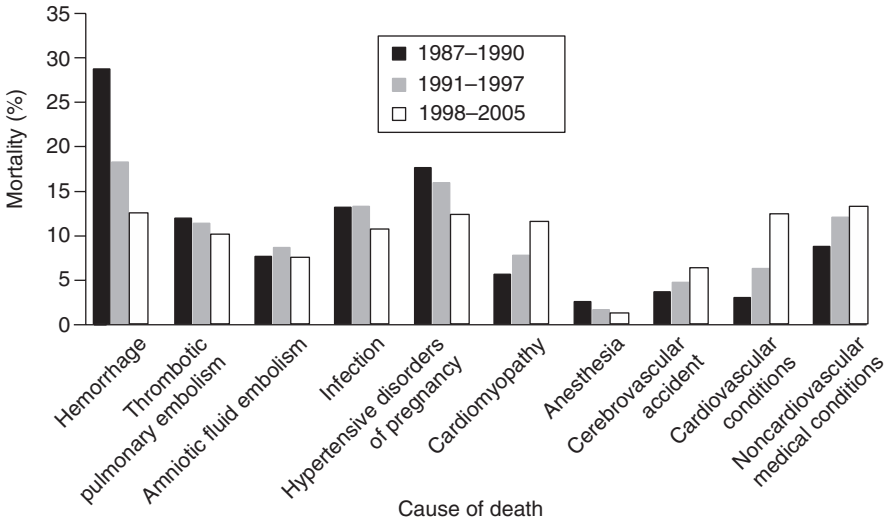

Fig. 8.1 Causes of maternal death in Japan and their prevalence in each era

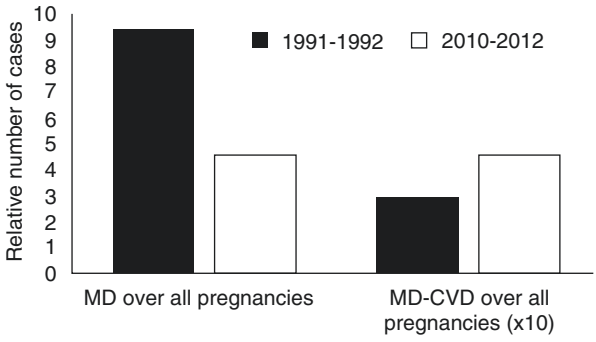

Fig. 8.2 Maternal mortality rate per 100,000 in Japan in 1991–1992 and 2010–2012. *MD* maternal death, *CVD* cardiovascular disease

8.3.3.1 The Maternal Background in the Deaths from CVD

The maternal background, age, and type of CVD are shown in Table 8.1 [8]. The entire range of childbearing ages was represented (19–39 years), and 66.7% of women were primigravida. Death occurred during the antepartum (6/15, 40.0%) and the postpartum periods (9/15, 60.0%). Whereas delivery failed in 33.3% of the cases, the mode of delivery for the remaining mothers was vaginal (5/15, 33.3%) or cesarean section (5/15, 33.3%).

8.3.3.2 Maternal Death from Aortic Dissection

The cases of maternal death from CVD related to aortic dissection were further analyzed with respect to the Stanford classification and family history of connective tissue disease (Table 8.2) [8]. Four cases were classified as type A, whereby the dissection affected the ascending aorta and the arch, rather than sections beyond the

Table 8.1 Background of maternal deaths related to cardiovascular disease in Japan in 2010–2012

Case no.	Cardiovascular disease	Age	Parity	Time of death	Maternal complication	History	Delivery mode
1	Aortic dissection	34	0	Postpartum day 4	–	–	CS
2	Aortic dissection	31	0	Gestational week 19	–	–	ND
3	Aortic dissection	36	1	Postpartum day 53	Marfan syndrome	–	CS
4	Aortic dissection	28	0	Gestational week 35	–	Post-PDA operation	CS
5	Aortic dissection	39	0	Gestational week 34	–	–	ND
6	Peripartum cardiomyopathy	21	0	Postpartum day 1	IDS	–	CS
7	Peripartum cardiomyopathy	34	1	Immediately after birth	–	–	VD
8	Peripartum cardiomyopathy	23	0	Postpartum day 15	–	–	VD
9	Sudden arrhythmic death syndrome	35	1	Gestational week 23	Long QT syndrome	–	N D
10	Sudden arrhythmic death syndrome	19	0	Postpartum day 82		–	VD
11	Acute cardiomyopathy	33	3	Gestational week 33	Schwannoma	–	ND
12	Acute cardiomyopathy	21	0	Gestational week 28	Depression	–	NO
13	Myocardial infarction	28	5	Immediately after birth		–	VD
14	Dissection of vertebral artery	35	0	Postpartum day 7	Pulmonary hypertension	–	CS
15	Pulmonary hypertension	20	0	Postpartum day 7	Pulmonary hypertension	–	VD

CS cesarean section, *IDS* integration dysfunction syndrome, *ND* no delivery, *PDA* patent ductus arteriosus, *VD* vaginal delivery

brachiocephalic vessels. In case 3, aortic dissection was caused by Marfan syndrome diagnosed before pregnancy. In cases 1 and 2, there was no family history or confirmed diagnosis of Marfan syndrome, but the patients exhibited physical features consistent with the disorder, namely, the typical tall and slender build. On the other hand, in cases 4 and 5, the patients did not have familial histories or physical features of Marfan syndrome. However, none of these cases (1, 2, 4, and 5) were autopsied or tested for genetic markers for Marfan syndrome before pregnancy. Among the cases of aortic dissection, in cases 1, 2, and 4, the first sign of complication was a prodrome of dorsal pain followed by cardiac arrest after 10 h, 1 h 10 min,

Table 8.2 Maternal background-related connective tissue disease for the five cases of maternal death with aortic dissection in Japan in 2010–2012

Case no.	Stanford classification type	Familial history suggestive of connective tissue disease	Medial history suggestive of connective tissue disease	Autopsy	Height (cm)
1	B	Unknown	Unknown	–	168
2	A	Unknown	Unknown	–	Unknown
3	A	Mother: Marfan syndrome	Marfan syndrome	+	168
4	A	–	–	–	153
5	A	–	–	+	153

and 48 h, respectively. In case 3, the first sign of complication was epigastric pain after cesarean delivery, and in case 5, the patient developed cardiac arrest without prodrome.

8.3.3.3 Death from Peripartum Cardiomyopathy

Three mothers died of cardiomyopathy, but none could be ascribed to a particular risk factor [8].

8.3.3.4 Death from Sudden Cardiac Arrest

A third of all 15 maternal deaths with CVD were sudden cardiac arrest. Whereas the patient in case 9 was diagnosed with long QT syndrome, the patient in case 10 had premature ventricular contraction in early pregnancy. The cause of death of those patients was deemed to be sudden adult/arrhythmic death syndrome because there was no known underlying condition to explain the sudden cardiac arrest, other than arrhythmia. Autopsies revealed that in case 11, the patient died of sudden cardiac arrest during treatment for a urinary tract infection, whereas in case 12, the patient died of sudden cardiac arrest soon after complaining of breathing difficulties. Finally, in case 13, the patient died of sudden cardiac arrest soon after delivery. In this case, myocardial infarction was identified as the cause of death after discovery of complete blockages in the second and third vessels of the coronary artery.

8.3.3.5 Death from Pulmonary Hypertension

Two deaths from pulmonary hypertension were identified [8]. In case 14, the patient underwent intracardiac surgery to repair an atrioventricular septal defect before pregnancy. However, mitral stenosis persisted, which led to the development of secondary pulmonary hypertension during pregnancy, then death. In contrast, case 15 was diagnosed with pulmonary hypertension at 40 gestational weeks after exhibiting difficulty breathing. Pulmonary hypertension worsened after delivery and the patient died a week later [8].

8.3.3.6 Timing of Occurrence of Maternal Death

Maternal death from CVD occurred more in the third trimester (33.3%) and the postpartum period (40.0%) than in earlier trimesters (13.3%). The proportion of maternal death from CVD with respect to all maternal death is shown in Fig. 8.3a, b.

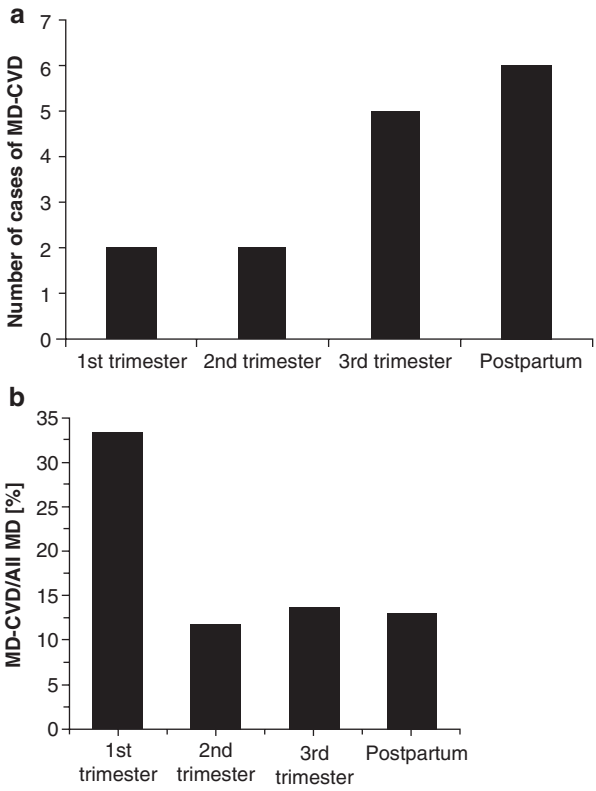

Fig. 8.3 (**a**) Frequency distribution of the time of death for the cases of maternal deaths related to cardiovascular disease in Japan in 2010–2012. (**b**) Percentage of maternal deaths related to cardiovascular disease with respect to all maternal deaths in that particular period. *MD* maternal deaths, *CVD* cardiovascular disease

8.4 Summary

The maternal death ratio in Japan has declined over the past 20 years. The five most prevalent etiologies of maternal death are obstetric bleeding, cerebral hemorrhage, amniotic embolism, thromboembolism, and CVD. The prevalence of maternal death from CVD increased significantly, despite death from other causes having decreased. These facts are partially consistent with the reported increase in maternal death-related venous embolism reported in Japan. One of the possible explanations is that the number of women with CVD reaching childbearing age has increased due to recent therapeutic and surgical advances. Especially, survival of women with congenital heart disease has increased, enabling them to reach reproductive age: In addition, incidences of atherosclerosis, obesity, diabetes, and hypertension have also increased, adversely affecting the tolerance of hemodynamic fluctuations and hypercoagulable states associated with pregnancy. Furthermore, the fact that more pregnancies are now started at an older age, due to the feasibility of effective fertility treatments, is also a possible contributing factor to the increased incidence of maternal death—CVD. From the preventive medical point of view, women with a history of CVD should be counseled cautiously regarding the life-threatening risks of pregnancy, both for them and the unborn child. During pregnancy, all women

should be closely monitored for early signs of maternal death—CVD—by using readily available screening tools, such as echocardiography, Holter monitoring, and the levels of brain natriuretic peptides, especially during the third trimester. In addition, it is important to trace women at risk of CVD during at least 3 months after the end of delivery to avoid late maternal death—CVD—as instability in the cardiovascular system persists until then. In summary, the rate of maternal death—CVD—has increased in Japan since the early 1990s. Thus, CVD and their risk factors should be closely monitored in pregnant women and documented in their relatives to improve counseling before the pregnancy, as well as the preventative management and treatment of pregnant woman.

References

1. Organization WH (2012) The WHO application of ICD-10 to deaths during pregnancy, childbirth and the puerperium: ICD-MM. World Health Organization, Geneva
2. Hogan MC, Foreman KJ, Naghavi M et al (2010) Maternal mortality for 181 countries, 1980–2008: a systematic analysis of progress towards Millennium Development Goal 5. Lancet 375:1609–1623
3. Khan KS, Wojdyla D, Say L et al (2006) WHO analysis of causes of maternal death: a systematic review. Lancet 367:1066–1074
4. Berg CJ, Callaghan WM, Syverson C et al (2010) Pregnancy-related mortality in the United States, 1998 to 2005. Obstet Gynecol 116:1302–1309
5. Confidential Enquiry into Maternal Death 2016. MBRRACE-UK: Mothers and babies: reducing risk through audits and confidential enquiries across the UK. https://www.npeu.ox.ac.uk/downloads/files/mbrraceuk/reports/MBRRACE-UK%20Maternal%20Report%202016%20-%20website.pdf. Accessed 30 Sept 2018
6. Nagaya K, Fetters MD, Ishikawa M et al (2000) Causes of maternal mortality in Japan. JAMA 283:2661–2667
7. Hasegawa J, Sekizawa A, Yoshimatsu J et al (2015) Cases of death due to serious group A streptococcal toxic shock syndrome in pregnant females in Japan. Arch Gynecol Obstet 291:5–7
8. Tanaka H, Katsuragi S, Osato K et al (2016) The increase in the rate of maternal deaths related to cardiovascular disease in Japan from 1991-1992 to 2010-2012. J Cardiol 69:74–78

Dilated Cardiomyopathy

9

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Abstract

Women with preexisting cardiomyopathy, such as dilated cardiomyopathy, who are followed closely during pregnancy often tolerate pregnancy and delivery. Many symptoms of a normal pregnancy can mimic heart failure in the antepartum period, and repeated maternal echocardiographic imaging is necessary during pregnancy. Risk factors for adverse outcomes include functional status at baseline and severity of systolic dysfunction. Beta-blockers are generally safe during pregnancy, but some reports suggest that they can cause intrauterine growth restriction. Cardiac complications such as worsening heart failure accompanied by worsening left ventricular ejection fraction (LVEF), arrhythmias, and cerebrovascular accidents occur most commonly in late pregnancy, as well as in the first 16 months postpartum. The level of brain natriuretic peptide (BNP) can be used to risk stratify women for adverse events. Pregnant women with dilated cardiomyopathy should be followed closely by a multidisciplinary team comprised of nurses, obstetricians, neonatologists, cardiologists, anesthesiologists, and cardiac surgeons. The team should ideally discuss a delivery plan prior to commencement of labor, with identification of the type of labor, anesthesia, and need for invasive hemodynamic monitoring.

Keywords

Pregnancy · Dilated cardiomyopathy · Ejection fraction · NYHA class

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9.1 Definition

Dilated cardiomyopathy (DCM) is defined based on the presence of typical symptoms of heart failure, left ventricular (LV) dilation, and LV systolic dysfunction of unknown origin.

9.2 Pathological Etiology

The pathological etiology of DCM is acute myocardial inflammation or chronic fibrosis and diffuse loss of cardiac myocytes. This can lead to dilation and thinning of the ventricular walls and a fall in ventricular systolic function reflected by a depressed ejection fraction (EF) [1]. DCM may be asymptomatic for several years. Presentation usually occurs late in the disease course with any one of the following symptoms:

- *Heart failure*. Symptoms include congestion (edema, orthopnea, paroxysmal nocturnal dyspnea) and reduced cardiac output (fatigue, dyspnea on exertion) [2, 3].
- *Arrhythmias and conduction system disease*. These commonly accompany advanced cardiomyopathy and heart failure. Genetic causes (e.g., pathogenic variants in *LMNA, SCN5A, DES*) may lead to prominent conduction system disease or arrhythmias out of proportion to the degree of LV dysfunction [4–7].
- *Thromboembolic disease*. Stroke or systemic embolus, secondary to LV mural thrombus, may also occur [2, 3]. Differentiation from peripartum cardiomyopathy (PPCM) is supported by the time of manifestation. If not known before conception, the condition is often unmasked during the first or second trimester when the hemodynamic load is increasing.

Onset usually occurs in adults in the fourth to sixth decade, although DCM may present in the fetal period, infancy, early or late childhood, adolescence, and elderly. Extensive additional background information is available.

9.3 Epidemiology of DCM-Complicated Pregnancy

The prevalence of DCM in the USA is 36 cases per 100,000 people and the disease is more common in African-Americans compared to Caucasians [8]. The prevalence of DCM among women of childbearing age is low. DCM includes a range of diverse myocardial processes, including myocarditis, ischemic heart disease, familial cardiomyopathy, and toxins such as alcohol or cocaine. Women of childbearing age may develop cardiomyopathy related to cancer therapies, such as doxorubicin, which is used for treatment of leukemia, lymphoma, and breast cancer, among other malignancies. Up to half of all cases of DCM are considered

idiopathic [8]. In the registry of the European Society of Cardiology, 1321 pregnancies complicated with structural or ischemic heart diseases were analyzed between 2007 and 2011, of which 32 cases (2.4%) were dilated cardiomyopathy. There was one maternal death in the 32 cases at 5 weeks postpartum [9]. In India, 10 patients (0.7%) had DCM out of 1472 patients with heart disease in pregnancies studied from 1994 to 2010 [10].

9.4 Pregnancy Outcomes

In Japan, 29 pregnancies with DCM were studied retrospectively from January 1985 to December 2010. Patients were divided into a poor prognosis group ($n = 6$; death or end-stage heart failure of the New York Heart Association (NYHA) class III and IV) and a good prognosis group ($n = 23$; all other cases) [11]. DCM was initially diagnosed during pregnancy in 6/6 and 8/23 patients in the poor and good prognosis groups, respectively ($P < 0.005$). The %FS of the first test during pregnancy was 17.5 ± 6.2 and 27.4 ± 9.3% in the respective groups ($P < 0.005$). In eight abortion cases with %FS 15.2 ± 3.1%, cardiac function and NYHA class were maintained until 20 months after abortion. There was no relationship between left ventricle end-diastolic dimension (LVEDD) and maternal outcome. It was concluded that onset during pregnancy and decreased EF (<40%) are risk factors for a poor maternal outcome in patients with DCM. Abortion prevents further deterioration of cardiac function in patients with a very low EF.

In Canada, 36 pregnancies (32 women) complicated with DCM from 1994 to 2008 were studied retrospectively [12]. Cardiac outcomes were compared with nonpregnant women with DCM ($n = 18$) matched by age and LV systolic function. Fourteen of the pregnancies (39%) were complicated by at least one maternal cardiac event. In multivariate analysis, moderate or severe LV dysfunction and/or NYHA functional class III or IV ($p = 0.003$) were the main determinants of adverse maternal cardiac outcomes during pregnancy. It was concluded that moderate to severe LV dysfunction and NYHA class III or IV are risk factors for cardiac events in DCM-complicated pregnancy.

9.5 Risks for Poor Pregnancy Outcomes

The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology recommends maternal risk assessment according to the modified WHO risk classification, in which patients with mild LV impairment are classified in the WHO II–III category, while those in NYHA III–IV and/or with EF < 30% are classified as WHO IV [13]. The risk for maternal morbidity or mortality is small, significant, and extremely high for WHO II, IIII, and IV categories, respectively [14].

9.6 Medical Management of Heart Failure During Pregnancy

As in nonpregnant patients, treatment of heart failure during pregnancy should be aimed at regulation of heart rate, reducing pre- and afterload, and increasing contractile capacity [15]. Due to fetotoxicity, conventional drugs used for treatment of heart failure, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and aldosterone antagonists, should not be used during pregnancy because they are toxic to the fetal kidney, show teratogenicity in congenital heart disease, and decrease amniotic fluid volume [16, 17]. Ideally, these drugs should be discontinued in women who are planning to become pregnant or as soon as pregnancy is confirmed.

Women who are planning to become pregnant must weigh the risks of discontinuation of drugs that prolong survival in the setting of LV dysfunction against the potential for teratogenicity, which is present throughout pregnancy, even during the first trimester. Women taking beta-blockers for treatment of chronic heart failure should continue to take these drugs during pregnancy, even if asymptomatic. Vasodilator therapy, when necessary, can be achieved with hydralazine or amlodipine, because there are published data supporting the safety of these drugs in pregnancy, particularly in the setting of hypertension [18]. Sodium restriction is recommended for all patients, whereas loop diuretics are indicated for symptomatic relief of significant peripheral edema or pulmonary congestion. Digoxin can be added or continued during pregnancy for symptomatic relief of heart failure symptoms, after beta-blockers and vasodilators have been maximized. For acute decompensation of heart failure, particularly if severe, therapy is used similarly to that in nonpregnant women. Intravenous diuretics and intravenous vasodilator therapy with nitroglycerin can be used safely. Right heart catheterization might be necessary if diagnosis of heart failure is difficult based on physical examination or when large shifts in hemodynamic status are anticipated (as in labor and delivery). However, right heart catheterization is not commonly used during pregnancy.

In a recent Japanese retrospective study of pregnancy with cardiovascular disease, the rates of fetal growth restriction were 7%, 26%, and 3% in alpha/beta-adrenergic blocker, beta-adrenergic blocker, and control groups, respectively ($p < 0.05$), with different rates of fetal growth restriction with each beta-blocker: atenolol, propranolol > metoprolol, and bisoprolol [19]. The use of beta-blockers has been associated with an increased risk of growth retardation and fetal/neonatal bradycardia, but guidelines suggest that their potential benefit may justify their use (preferably β1, except atenolol) [20].

A case report in Belgium showed good results with hydralazine during pregnancy in a 36-year-old patient with ischemic cardiomyopathy (EF 37%, LVEDD 62 mm, NYHA III). The patient was in WHO category II–III for maternal risk [14]. Dyspnea of NYHA class III developed in the fourth month, and EF declined to 30% without signs of congestion; therefore, hydralazine12.5 mg three times a day (TID) was started. Echocardiography at 6 months showed a stable EF (28%) without LV dilatation or a change in symptoms. Hydralazine was well tolerated and the dose

was increased to 25 mg TID. The patient remained stable thereafter until the 37th week, when she developed mild peripheral edema. Labor was induced in the 38th week with epidural analgesia, and a healthy baby was delivered vaginally with vacuum extraction. Breast-feeding was discouraged and conventional heart failure treatment was reinitiated 1 day postpartum. Two years later, the patient remained stable (NYHA II, EF 35%, LVEDD 60 mm) [15].

9.7 Clinical Findings During Pregnancy

A physical examination in a healthy pregnancy can often mimic disease [11, 21]. Increased plasma volume might result in a systolic flow murmur, which can be heard in most healthy pregnant patients. This murmur is usually systolic and soft (usually grade II/VI). Moreover, distended or mildly increased neck veins, mild lower-extremity edema, and tachycardia are normal, common findings. In addition, common complaints of a healthy pregnancy, such as palpitations, fatigue, decreased exercise tolerance, and orthopnea, are often identical to those in occult or overt heart failure. During pregnancy, some patients might require careful follow-up evaluations that might increase in frequency according to symptoms or severity of disease. Repeat echocardiography, perhaps as often as once per trimester or sooner as clinically indicated, can be helpful because many symptoms of a healthy pregnancy can mimic heart failure in the antepartum period. Due to an inability to increase cardiac output in a setting of expanded intravascular blood volume, patients with an underlying cardiomyopathy often develop clinical heart failure, and therefore ongoing surveillance is important. Patients with LV dysfunction might require restriction of activities, inpatient observation before delivery, and initiation or alteration of drug therapy.

9.7.1 Biomarkers in Pregnancy

Limited data are available on the utility of serum BNP or N-terminal pro B-type natriuretic peptide (NT-proBNP) levels in pregnancy. In a small series of healthy pregnant women, there were no significant differences in mean BNP levels at various stages of pregnancy and in the postpartum period [22–24]. However, pregnant women had BNP levels that were approximately twice as high as nonpregnant women, although within the normal range. In women with preeclampsia, levels of circulating atrial natriuretic peptide and BNP are directly related to changes in LV mass and volume [25]. BNP levels in women with severe preeclampsia are significantly higher than those in a healthy population, reflecting greater ventricular wall stress associated with this condition, and BNP is now widely used to screen for ventricular dysfunction [23]. In a small series of pregnant women with preeclampsia, diastolic LV function was impaired, and NT-proBNP was increased, compared with data in normal pregnancies [26]. In a more recent study, BNP was higher in pregnant women with heart disease than in those without heart disease [27]. In

addition, among women with clinical events, all were found to have elevated BNP, whereas women with BNP ≤100 pg/ml had no events. Thus, BNP had a negative predictive value of 100% for identifying events during pregnancy in this small series. However, a subset of women without any clinical events had elevated BNP, a finding of unclear significance. Most healthy pregnant women have low and stable BNP levels throughout pregnancy, suggesting that these women are able to compensate for the hemodynamic load of pregnancy. Although limited clinical data are available, measurement of BNP or NT-proBNP levels seems to have clinical utility in cases in which diagnosis of heart failure is in question [26].

9.8 Timing of Delivery

A multidisciplinary team is crucial for management of patients with DCM at the time of labor and delivery. Consultation among obstetricians, obstetrical anesthesiologists, and cardiologists is recommended before initiation of labor and delivery. In addition, patients with heart failure or underlying cardiomyopathy should be monitored carefully throughout labor and delivery, as well as in the early postpartum period, when hemodynamic decompensation is most likely to occur (for management during labor and delivery, see Table 9.1). This includes continuous maternal electrocardiographic monitoring and noninvasive blood pressure monitoring. Invasive central monitoring, such as right heart catheterization and arterial line monitoring, can be used on an individual basis. Arterial line monitoring is considered helpful and low-risk. Right heart catheterization, although not required, might be needed to optimize hemodynamic status when large shifts in volume are anticipated, such as during Cesarean section or when there is evidence of clinical instability [28]. There are no official recommendations, but right heart catheterization is occasionally used in pregnant women with severe clinical heart failure or severely reduced LV systolic function at the time of delivery.

A decision on the timing and mode of delivery depends on the hemodynamic status of the patient and on the response to drug therapy. Early delivery is not required in all patients with cardiomyopathies or heart failure. The timing of delivery for a critically ill patient with heart failure requires a coordinated decision among cardiologists, obstetricians, and anesthesiologists that balances the risks to

Table 9.1 Decision regarding timing and mode of delivery

1.	Management during labor and delivery and postpartum concerns
2.	Short vaginal delivery with excellent anesthesia, with consideration of an assisted second stage of labor
3.	Left lateral decubitus position
4.	Cesarean section per obstetric indications
5.	Invasive monitoring if needed (right heart catheterization, invasive arterial blood pressure monitoring)
6.	Medical therapy optimization of loading conditions
7.	Monitoring and treatment of pulmonary edema

the mother and fetus of continuing the pregnancy with the risk of delivery and how that delivery should occur. If the heart failure is refractory to drug therapy, delivery should be strongly considered. The lack of official recommendations requires the use of an individualized approach. Almost all women with cardiac disease should attempt vaginal delivery, unless obstetric contraindications exist. For women with preexisting cardiac disease, vaginal delivery poses less cardiac risk because Cesarean delivery is accompanied by approximately twice as much blood loss.

Patients who are considered stable from a cardiac perspective can be allowed to progress spontaneously through the various stages of labor. However, if there are concerns about the functional adequacy of the heart and circulation, labor can be induced under controlled conditions. The timing of induction can be individualized, taking into account the cardiac status of the patient, inducibility of the cervix, and fetal lung maturity. From a practical point of view, it is useful to plan the induction so that delivery occurs at a time when all services are available. In general, a long induction in a woman with an unfavorable cervix should be avoided. Induction of labor in a patient with a favorable cervix usually requires only oxytocin administration and artificial rupture of membranes. An unfavorable cervix, however, should be treated with a prostaglandin E analog. Even this should be done cautiously in women with underlying cardiomyopathies because prostaglandin analogs might be absorbed systemically, causing unwanted hemodynamic consequences, including decreased systemic vascular resistance and reflex tachycardia [29]. In a recent study of patients with dilated cardiomyopathy, most deliveries were vaginal (81%), and the most frequently used form of anesthesia was epidural anesthesia (86%) [12]. Indications for Cesarean delivery were unrelated to preexisting cardiac disease in all these patients. As expected, the rates of fetal/neonatal events were higher in women with at least one obstetric risk factor, including a history of premature delivery or rupture of membranes, an incompetent cervix, or a need for Cesarean delivery. Smoking, anticoagulant use, multiple gestation, and maternal age < 20 or > 35 years were non-obstetric risk factors associated with an increased rate of fetal/neonatal events.

9.9 Anesthetic Management During Labor (→See Chap. 3)

Anesthetic considerations in pregnant women with chronic or new-onset heart failure require a specialized approach and, when possible, should be planned in the antepartum period. Women with cardiomyopathy or evidence of clinical heart failure should not expect a natural childbirth without the use of some form of anesthesia when vaginal delivery is selected. The goal of the anesthesia is to blunt the physiological increase in metabolic demands and hemodynamic stress that normally accompanies labor and delivery. The goals of management are mainly to avoid excessive anesthetic-induced myocardial depression, maintain normovolemia, and minimize the inherent sympathetic stimulation associated with labor [30].

A combination of intravenous opiates and lumbar epidural anesthesia is effective for relief of pain during labor and delivery, and this is considered to be the approach of choice. Epidural anesthesia, if introduced slowly and carefully, produces changes in preload and afterload that can be advantageous in the setting of reduced ventricular function. This approach also provides excellent operative analgesia, thus limiting pain-induced elevation of sympathetic activity, but also reduces the maternal urge to push (Valsalva maneuver). Additionally, accompanying venodilation reduces venous return, which might also be favorable for patients with evidence of volume overload. A decrease in systolic blood pressure might require treatment with vasoactive agents, rather than intravenous fluids. Alternatively, the use of general anesthesia has the risk of hemodynamic instability associated with systemic anesthetic administration and requires adequate sedatives for tolerance of endotracheal intubation.

Once in labor, women with cardiac disease should be placed in a left lateral decubitus position to avoid inferior vena cava (IVC) compression by the gravid uterus. The obstetrician should allow the fetal head to descend to the perineum without maternal assistance, in an attempt to avoid the undesirable circulatory effects of the Valsalva maneuver. The second stage of labor can be shortened via assistance with low forceps or by vacuum extraction as needed. Throughout this process, the clinical scenario should dictate the need to abandon vaginal delivery and proceed with Cesarean delivery.

9.10 Postpartum Complications

After delivery, uterine bleeding is controlled naturally by continued uterine contractions from posterior pituitary oxytocin secretion. Synthetic oxytocin is often administered to augment these effects, but should be infused slowly to avoid hypotensive effects. Hemodynamic monitoring of the mother should continue for at least 12–24 h after delivery because volume redistribution during this period causes rapid intravascular volume shifts. If severe anemia is present, often related to dilutional anemia of pregnancy exacerbated by blood loss at delivery, treatment with iron supplementation or blood transfusion can be considered in an effort to relieve tachycardia and decrease myocardial work. Inciting events are difficult to define, but pregnancy seems to affect the natural history of DCM, particularly in the short term [12]. Cardiac complications such as worsening heart failure accompanied by worsening LVEF, arrhythmias, and cerebrovascular accidents occur most commonly late in pregnancy, as well as in the first 16 months postpartum. The third trimester and early postpartum periods are times of maximum hemodynamic change, supporting the concept that accelerated changes in hemodynamic load can precipitate cardiac decompensation. Even beyond hemodynamic fluctuations, a transient decline in LV contractility during pregnancy has been described, which might be more important in patients with poor cardiac reserve [31]. Also, this decline in LV systolic function might not be reversible. An important issue seems to be continuation of optimal medical therapy for heart failure during pregnancy, which is not possible secondary to the

teratogenic effects of ACE-Is and ARBs. The hemodynamic load of pregnancy and delivery, coupled with prolonged discontinuation of optimal medical therapy during pregnancy, often because of contraindications or patient preference, might also predispose the patient to further late negative effects on ventricular function [12, 32].

9.11 Anticoagulation Therapy

The risk for thromboembolic phenomena is increased during pregnancy and further increased in a setting of cardiomyopathy with severely reduced ventricular function. The incidence of thromboembolic complications in pregnant women with cardiomyopathy is not known, but several reports of thromboembolic phenomena in women with PPCM suggest that the risk is high. Anticoagulation therapy should be considered for all pregnant and postpartum women with cardiomyopathy and LVEF <35%. Unfractionated heparin and low-molecular-weight heparin (risk category C) do not cross the placenta and are safe to use during pregnancy. Warfarin is a risk category D drug that should be avoided during pregnancy, although it is considered safe during breast-feeding.

References

1. Bernstein PS, Magriples U (2001) Cardiomyopathy in pregnancy: a retrospective study. Am J Perinatol 18:163–168
2. Burkett EL, Hershberger RE (2005) Clinical and genetic issues in familial dilated cardiomyopathy. J Am Coll Cardiol 45:969–981
3. Sivasankaran S, Sharland GK, Simpson JM (2005) Dilated cardiomyopathy presenting during fetal life. Cardiol Young 15:409–416
4. Judge DP (2009) Use of genetics in the clinical evaluation of cardiomyopathy. JAMA 302:2471–2476
5. Dellefave L, McNally EM (2010) The genetics of dilated cardiomyopathy. Curr Opin Cardiol 25:198–204
6. Hershberger RE, Morales A, Siegfried JD (2010) Clinical and genetic issues in dilated cardiomyopathy: a review for genetics professionals. Genet Med 12:655–667
7. Hershberger RE, Siegfried JD (2011) State of the art review. Update 2011: clinical and genetic issues in familial dilated cardiomyopathy. J Am Coll Cardiol 57:1641–1649
8. Yancy CW, Jessup M, Bozkurt B et al (2013) 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 62(16):e147–e239
9. Roos-Hesselink J, Ruys T, Stein J, Thilén U, Webb G, Niwa K et al (2013) Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. Eur Heart J 34:657–665
10. Vanita S, Neelam A, Arun K, Seema C, Pooja S, Rajesh V (2013) Pregnancy with dilated and peripartum cardiomyopathy: maternal and fetal outcome. Arch Gynecol Obstet 287:195–199
11. Katsuragi S, Omoto A, Kamiya C, Ueda K, Sasaki Y, Yamanaka K et al (2012) Risk factors for maternal outcome in pregnancy complicated with dilated cardiomyopathy. J Perinatol 32:170–175
12. Grewal J, Siu S, Ross H, Mason J, Balint O, Sermer M et al (2010) Pregnancy outcomes in women with dilated cardiomyopathy. J Am Coll Cardiol 55:45–52

13. European Society of Gynecology (ESG), Association for European Paediatric Cardiology (AEPC), German Society for Gender Medicine (DGesGM), Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, Gibbs JS, Gohlke-Baerwolf C, Gorenek B, Iung B, Kirby M, Maas AH, Morais J, Nihoyannopoulos P, Pieper PG, Presbitero P, Roos-Hesselink JW, Schaufelberger M, Seeland U, Torracca L, ESC Committee for Practice Guidelines (2011) ESC guidelines on the management of cardiovascular diseases during pregnancy: the task force on the management of pregnancy of the European Society of Cardiology (ESC). Eur Heart J 32:3147–3197
14. Thorne S, MacGregor A, Nelson-Piercy C (2006) Risks for contraception and pregnancy in heart disease. Heart 92:1520–1525
15. Gevaert S, Paum M, Tromp F, Ascoop A, Roelens K et al (2014) Treatment of pre-existing cardiomyopathy during pregnancy. Acta Cardiol 69:193–196
16. Cooper WO, Heenandez-Diaz S, Arbogast PG, Dudly JA, Dyer S, Gideon PS et al (2006) Major congenital malformations after first-trimester exposure to ACE inhibitors. N Engl J Med 354:2443–2451
17. Messina M, Biffignandi P, Ghigo E, Jeanter MG, Molinatti GM (1979) Possible contraindication of spironolactone during pregnancy. J Endocrinol Investig 2:222
18. Widerhorn J, Rubin JN, Frishman WH, Elkayam U (1987) Cardiovascular drugs in pregnancy. Cardiol Clin 5:651–674
19. Tanaka K, Tanaka K, Tanaka H, Kamiya C, Katsuragi S, Sawada M et al (2016) Beta-blockers and fetal growth restriction in pregnant women with cardiovascular disease. Circ J 80:2221–2226
20. Meidahl PK, Jimenez SE, Andersen JT, Petersen M, Brodbaek K, Kober L et al (2012) β-blocker treatment during pregnancy and adverse pregnancy outcomes: a nationwide population-based cohort study. BMJ Open 2:e001185
21. Kathleen S, Elaine S, Travis B (2011) Pregnancy in patients with pre-existing cardiomyopathies. J Am Coll Cardiol 58:337–350
22. Hameed AB, Chan K, Ghamsary M, Elkayam U (2009) Longitudinal changes in the B-type natriuretic peptide levels in normal pregnancy and postpartum. Clin Cardiol 32:E60–E62
23. Resnik JL, Hong C, Resnik R et al (2005) Evaluation of B-type natriuretic peptide (BNP) levels in normal and preeclamptic women. Am J Obstet Gynecol 193:450–454
24. Folk JJ, Lipari CW, Nosovitch JT, Silverman RK, Carlson RJ, Navone AJ (2005) Evaluating ventricular function with B-type natriuretic peptide in obstetric patients. J Reprod Med 50:147–154
25. Borghi C, Esposti DD, Immordino V et al (2000) Relationship of systemic hemodynamics, left ventricular structure and function, and plasma natriuretic peptide concentrations during pregnancy complicated by preeclampsia. Am J Obstet Gynecol 183:140–147
26. Rafik Hamad R, Larsson A, Pernow J, Bremme K, Eriksson MJ (2009) Assessment of left ventricular structure and function in preeclampsia by echocardiography and cardiovascular biomarkers. J Hypertens 27:2257–2264
27. Tanous D, Siu SC, Mason J et al (2010) B-type natriuretic peptide in pregnant women with heart disease. J Am Coll Cardiol 56:1247–1253
28. Howlett JG, McKelvie RS, Costigan J et al (2010) The 2010 Canadian Cardiovascular Society guidelines for the diagnosis and management of heart failure update: heart failure in ethnic minority populations, heart failure and pregnancy, disease management, and quality improvement/assurance programs. Can J Cardiol 26:185–202
29. Secher NJ, Thayssen P, Arnsbo P, Olsen J (1982) Effect of prostaglandin E2 and F2alpha on the systemic and pulmonary circulation in pregnant anesthetized women. Acta Obstet Gynecol Scand 61:213–218
30. Siu SC, Sermer M, Harrison DA et al (1997) Risk and predictors for pregnancy-related complications in women with heart disease. Circulation 96:2789–2794
31. Geva T, Mauer MB, Striker L, Kirshon B, Pivarnik JM (1997) Effects of physiologic load of pregnancy on left ventricular contractility and remodeling. Am Heart J 133:53–59
32. Pryn A, Bryden F, Reeve W, Young S, Patrick A, McGrady EM (2007) Cardiomyopathy in pregnancy and caesarean section: four case reports. Int J Obstet Anesth 16:68–73

Hypertrophic Cardiomyopathy

10

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Abstract

In many cases with stable hypertrophic cardiomyopathy (HCM), the prognosis for pregnancy is comparatively favorable. However, heart failure, defined as New York Heart Association (NYHA) class III–IV, left ventricular ejection fraction <35–40%, and left ventricular outflow tract obstruction with mean pressure gradient >40–50 mmHg, requires strict caution during pregnancy or advice on avoidance of pregnancy. In pregnancy in these cases, caution should be exercised when circulating blood volume reaches its peak at around 30 gestational weeks, due to the high frequency of symptoms, especially increases in arrhythmia and pulmonary congestion.

Keywords

Hypertrophic cardiomyopathy · Inherited cardiomyopathy · β-blocker

10.1 Definition

Cardiomyopathy was classically defined as a myocardial disease that is associated with cardiac dysfunction [1] by the World Health Organization/International Society and Federation of Cardiology (WHO/ISFC) Task Force in 1995. The disease is classified into five types: dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular cardiomyopathy, and unclassified cardiomyopathy [1]. HCM is defined as a disease

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in which there is abnormal hypertrophy in the left and/or right ventricular myocardium, despite there being no clear causal factors of cardiac hypertrophy, such as valvular disease or hypertension.

10.2 Basic Pathology

HCM is a disease with left or right ventricular hypertrophy, characteristically non-uniformly and without a clear cause. Moreover, there is generally no expansion of the left ventricular (LV) cavity, and LV contraction is normal or excessive. The principal pathological feature of HCM is a reduction in LV diastolic performance due to cardiac hypertrophy [2].

- Particularly in cases with obstruction of the LV outflow tract, hypertrophic obstructive cardiomyopathy (HOCM) is diagnosed.
- Variations of HOCM with region-specific hypertrophy include midventricular obstruction (hypertrophy associated with stenosis in the midventricular cavity) and apical hypertrophic cardiomyopathy (hypertrophy localized to the ventricular apex).
- Over the course of HCM, thinning of the hypertrophic ventricular wall may cause expansion of the ventricular cavity accompanied by a reduction in LV diastolic performance, thereby giving a dilated cardiomyopathy-like pathology that is referred to as the dilated phase of hypertrophic cardiomyopathy (D-HCM). While this diagnosis is definite if the course is being observed, it may also be diagnosed in cases where a prior positive diagnosis of HCM was made, even if follow-up is not performed.

During pregnancy, pregnancy-related physiological alterations need to be considered, in addition to these basic pathologies. When pregnancy is complicated by HCM, pregnancy-based increases in circulating plasma volume and decreases in systemic vascular resistance induce an increase in the systolic pressure gradient of the LV outflow tract, which subsequently increases mitral regurgitation, thus increasing the risk of congestive heart failure [3].

10.3 Symptoms

Some HCM patients are asymptomatic, but many present with symptoms pertaining to cardiac abnormality, most of which can be divided into chest and brain symptoms.

10.3.1 Myocardial Ischemia

Among chest symptoms, chest pain is extremely common. Pain or tightness in the chest is often caused by relative myocardial ischemia. Coronary vasospasm,

coronary stenosis, or the presence of peripheral disturbances in coronary circulation is also possible [4, 5]. Nitrates are contraindicated for severe HOCM patients; therefore, coronary angiography and selection of appropriate treatments are required when coronary abnormalities are implicated.

10.3.2 Heart Failure

Numerous patients also complain of dyspnea on exertion and/or difficulty breathing. It is thought that phenomena such as an elevation of pulmonary capillary pressure due to elevated LV end-diastolic pressure accompanied by LV diastolic impairment, and low cardiac output due to narrowing of the LV cavity, are closely associated with onset of dyspnea. In particular, a lack of increased cardiac output in response to heart rate increases associated with laborious activity is closely related to onset of dyspnea [6].

In pregnancy, chest symptoms are exacerbated by emergence of congestive heart failure, which is induced by elevated LV end-diastolic pressure due to an increase in the systolic pressure gradient of the LV outflow tract and/or severe LV diastolic dysfunction.

10.3.3 Arrhythmia and Sudden Death

Palpitation frequently arises from arrhythmia and tachycardia (i.e., an increase in contractile force in association with excessive contraction). Indeed, many HCM patients suffer from palpitation in association with supraventricular or ventricular arrhythmia. Palpitations may also be induced by paroxysmal or sustained atrial fibrillation; thus, examinations that utilize devices such as Holter electrocardiography are essential. Particularly in cases of HCM associated with atrial fibrillation (sustained or paroxysmal), there is a high rate of associated thromboembolism [7], and appropriate anticoagulant therapy is required.

Risk factors for sudden death in HCM are shown in Table 10.1 [2, 8–10]. Major risk factors include ventricular arrhythmia, syncope, a family history of sudden death, and marked LV hypertrophy, with factors such as D-HCM, LV outflow tract obstruction, and extensive fibrosis also contributing to the risk. Intense exercise or coronary artery disease may be modifiable risk factors, and transition to D-HCM or atrial fibrillation complications profoundly contributes to heart failure and stroke [11].

Changes in circulation dynamics during pregnancy are characterized by increases in circulating blood volume, pulse rate/stroke volume increase-based increases in cardiac output, and decreases in peripheral vascular resistance. Typically, in HCM, increased cardiac contraction force/increased preload/decreased afterload is an aggravating factor by which ventricular volume decreases and the LV outflow tract pressure gradient increases. Conditions such as increased

Table 10.1 Risk factors for sudden death (cited from two references)

Major risk factors
Cardiac arrest (ventricular fibrillation)
Spontaneous onset of sustained ventricular tachycardia
Family history of sudden death
Unexplained syncope
Marked left ventricular hypertrophy (left ventricular wall thickness ≥30 mm)
Non-sustained ventricular tachycardia on Holter electrocardiogram
Abnormal blood pressure response to exercise
Possible risk factors
Dilated phase of hypertrophic cardiomyopathy
Ventricular apical aneurysm
Left ventricular outflow tract obstruction
Extensive late gadolinium enhancement pattern on magnetic resonance imaging
Atrial fibrillation
High-risk gene mutations
Modifiable risk factors
Intense exercise (competitive athletics)
Coronary artery disease

preload during pregnancy are changes analogous to those that occur during exercise. However, although intense exercise has been singled out as a modifiable risk factor of sudden death, it is not understood whether the same is true for pregnancy. Although sudden death has been described in cases of pregnancy complicated by HCM [12–17], all exhibited major risk factors for sudden death; thus, its association with pregnancy remains unclear.

10.3.4 Brain Symptoms

Important and common brain symptoms, such as dizziness, blackouts, and syncope, are thought to stem from cerebral ischemia, and these symptoms are important pre-existing disorders in HCM patients that are linked to sudden death [18]. Onset of these symptoms is frequent in patients with severe arrhythmia such as ventricular tachycardia [19], but they are not intrinsic to all arrhythmias [20]. Their rate of occurrence is high in patients with small LV cavities or a LV cavity pressure gradient. Occurrence of brain symptoms is also frequent under circumstances where stress on the LV wall is reduced, and these symptoms frequently occur when using contraindicated drugs, such as vasodilators, when consuming alcohol, or when transitioning from cold to warm places.

The frequency of arrhythmia is increased during and after pregnancy, and brain symptoms such as syncope may become more severe.

10.4 Heredity

10.4.1 Genetic Perspective in HCM

It is well established that HCM is hereditary. In 1990, a family line was identified in which a mutation in the MYH7 gene was shown to be the cause of disease [20]. Subsequently, >16 genes and 900 mutations have been identified as causes of HCM, and hereditary HCM is the cause of disease in ~50–60% of family lines. The frequency of HCM in which there is autosomal dominant heredity is shown in Table 10.2 [21–24]. Mutations in MYH7 and MYBPC3 genes occur with the highest frequency, and both genetic abnormalities are present in 75–80% of cases. Most genes implicated in the etiology of HCM are those that encode proteins for myocardial fiber/sarcomere formation. Strong myocardial hypertrophy induced by MYH7 and MYBPC3 mutations and mild hypertrophy due to TNNT2 mutations reduce myocardial contractile force, resulting in a relatively early transition to the dilated phase.

Even in isolated cases of HCM, mutations are identified 15% of the time. For HCM patients and their families, counseling is provided on hereditary patterns and clinical symptoms in cases where there are clear genetic abnormalities. Most causal genes in diseases with HCM-like pathologies have been characterized. Many of these diseases have a recessive mode of inheritance, and counseling becomes necessary for carriers and patients with Danon disease (lysosomal membrane protein deficiency) and Fabry disease (α-galactosidase deficiency). In heredity counseling, it is important to be aware of the strong tendency to perceive the topic of hereditary cardiomyopathy negatively. It is not infrequent that patients and families will have prior experience of someone contracting the disease within their family; therefore, a knowledge bias based only on this experience may exist. Therefore, it is essential that the latest medical information, such as improvements in prevention and treatment, are presented in an understandable manner.

10.4.2 Clinical Pathology and Genetic Background

The clinical pathology of HCM varies in severity, age of onset, and mutation penetrance, with identical mutations carried within families or within different maternal

Table 10.2 Genes involved in inherited hypertrophic cardiomyopathy (cited with occasional paraphrasing from two references)

Most frequently affected genes	Frequency (%)
MYH7 (β-myosin heavy chain)	30–40
MYBPC3 (myosin binding protein C)	30–40
TNNT2 (cardiac troponin T)	<5
TNNI3 (cardiac troponin I)	<5
TPM1 (α-tropomyosin)	<5

lines. In addition, variables such as environmental factors, sex, and factors relating to modification of genes contribute to clinical variation. However, making comparisons between genetic types and clinical forms is useful for patient understanding because there have been reports of cases in which the survival prognosis and other clinical factors differ depending on the genetic form. For example, myocardial β-myosin heavy chain (MYH7) mutation-based HCM has a comparatively young age of onset and a considerable degree of hypertrophy in many cases. Notably, in MYH7 Arg403Gln mutation-based HCM, sudden death and heart failure are frequent, and in MYH7 Arg719Trp-based HCM, heart failure is frequent. Previous reports on HCM varieties, such as those due to myocardial troponin T gene mutations, reveal that most cases present with a mild degree of hypertrophy. In HCM cases due to cardiac myosin binding protein C (MYBPC3) mutations, penetrance tends to be low, and the age of onset tends to be high [23, 25–31]. Variety is a characteristic of HCM, and many cases of sudden death have been reported in families in which the cause of disease is a mutation associated with a favorable prognosis. In contrast, minimal rates of disease-related death have been found in cases in families in which the cause of disease is a mutation associated with an unfavorable prognosis. Therefore, conjecture on survival prognosis based on gene mutations is limited [11, 25, 30].

10.5 Prognosis of HCM-Associated Pregnancy

The first report of pregnancy complicated by HCM was published by Turner et al. in 1968 [31]. This study included 13 pregnancies (9 women). All cases involved HOCM, but there were no cardiovascular events, and maternal prognosis was favorable. Furthermore, of the nine women, eight received oral β-blockers, which were thought to be possibly conducive to the favorable prognosis [31]. Oakley et al. published a subsequent report in 1979 on 43 pregnancies (23 women). In six women, diuretics were utilized due to emergence of respiratory impairment, and oral β-blockers were used in 18 pregnancies. Although oral β-blockers are recommended to protect mothers, they may also be associated with growth restriction and bradycardia [12]. Twenty years after these two reports, Siu et al. reported 546 cases of pregnancy complicated by heart disease, including 9 pregnancies involving HCM, 1 of which presented with ventricular tachycardia, and maternal prognosis was favorable [13]. In 2003, Thaman et al. published a comprehensive report on HCM-associated pregnancy [16], showing that 36 (28.3%) of 127 pregnancies had cardiac symptoms during pregnancy. However, >90% of these cases were symptomatic prior to pregnancy, and these symptoms did not subsequently increase in severity. Heart failure was confirmed in two (1.5%) of the pregnancies [16]. Based on these findings, the prognosis of pregnancy associated with stable HCM appears to be favorable. In 2014, Tanaka examined the period of cardiovascular events in HCM and found that these events frequently occurred during the first trimester and around the 30th week of pregnancy and that most events were arrhythmias. Drug administration prior to pregnancy was reportedly a risk factor for cardiovascular events during pregnancy.

Table 10.3 Reports on pregnancy with HCM

Year of publication	Author	Number of cases
1968	Turner et al.	9
1979	Oakley et al.	23
2001	Siu et al.	9
2002	Autore et al.	40
2003	Avila et al.	15
2003	Thaman et al.	127
2007	Avila et al.	23
2014	Tanaka et al.	27

Excluding case reports, there have been eight previous reports on HCM-associated pregnancy (Table 10.3), which taken together provide an overall and relatively favorable pregnancy prognosis for such cases. However, strict management is necessary due to the potentially elevated rate of cardiovascular events during pregnancy in cases in which symptoms were present or drugs were administered prior to pregnancy and in cases involving risk factors for sudden death.

10.6 High-risk Pregnancy Criteria

There are no specific criteria for determining if pregnancy should continue in cases of HCM. While onset of cardiovascular events during pregnancy and the risk of premature birth are high in cases where there are symptoms of chest pain/arrhythmia prior to pregnancy, or cases of high-grade LV outflow tract obstruction [11, 23], perinatal prognosis of pregnancy complicated by HCM is favorable under stable conditions. According to the Guidelines for Indication and Management of Pregnancy and Delivery in Women with Heart Disease (JCS 2010), cases of heart failure, defined as New York Heart Association (NYHA) class III–IV with LV ejection fractions <35–40% and LV outflow tract obstruction associated with high-grade aortic valve stenosis with an average pressure gradient >40–50 mm Hg, require strict caution in the event of pregnancy or make the avoidance of pregnancy strongly desirable [3]. Sudden death is known to occur in patients ≤35 years and in those with factors such as peak wall thickening >30 mm, prior cardiac arrest or sustained ventricular tachycardia, repeated syncope, or a family history of sudden death [3]. In such cases, careful consideration is necessary as to whether such patients are fit for pregnancy and childbirth.

10.7 Pregnancy Management

The pregnancy prognosis is relatively favorable except in high-risk cases, but attentive monitoring for arrhythmia or congestive heart failure during pregnancy is required. Patients are monitored during pregnancy for recent signs and symptoms, such as shortness of breath during laborious activity, palpitations, chest pain, and

syncope. In the event of such symptoms, oral administration of β-blockers is considered. Extra caution should be exercised when circulating blood volume reaches its peak around the 30th week of pregnancy due to the high rate of occurrence of symptoms, particularly increases in the severity of arrhythmia and congestive heart failure [17]. In cases of sustained atrial fibrillation, anticoagulant therapy is recommended.

10.8 Childbirth/Puerperal Management

In stable HCM, vaginal delivery is generally chosen, but caution is required as increases in the LV outflow pressure gradient are caused by decreased blood pressure due to epidural/vasodilation or decreased preload due to dehydration. In cases where obstetrically adapted Cesarean section is performed, if the case involves high-grade LV outflow tract obstruction, general anesthesia should be considered over epidural or subarachnoid anesthesia. Constraints or postures that reduce venous flow must be avoided, and in some cases shortening of the second stage of delivery via instrumental delivery should be considered. Caution is also required during the puerperal period as increases in venous flow induce an increase in cardiovascular events such as arrhythmia and pulmonary congestion [3].

References

1. Richardson P, McKenna W, Bristow M et al (1996) Report of the 1995 World Health Organization/International Society and Federation of Cardiology task force on the definition and classification of cardiomyopathies. Circulation 93:841842
2. JCS Joint Working Group (2016) Guidelines for diagnosis and treatment of patients with hypertrophic cardiomyopathy (JCS 2012). Circ J 80:753–774
3. JCS Joint Working Group (2012) Guidelines for indication and management of pregnancy and delivery in women with heart disease (JCS 2010): digest version. Circ J 76:240–260
4. Kodama K, Hamada M, Kazatani Y et al (1998) Clinical characteristics in Japanese patients with coexistent hypertrophic cardiomyopathy and coronary vasospasm. Angiology 49:849–855
5. Ogimoto A, Shigematsu Y, Nakura J et al (2005) Endothelial nitric oxide synthase gene polymorphism (Glu298Asp) in patients with coexistent hypertrophic cardiomyopathy and coronary spastic angina. J Mol Med 83:619–625
6. Mukai M, Hamada M, Sumimoto T et al (1988) Disparate difference in preload reserve between myocardial hypertrophy due to essential hypertension and hypertrophic cardiomyopathy. J Hypertens Suppl 6(suppl 4):s138–s140
7. Shigematsu Y, Hamada M, Suzuki M et al (1995) Mechanism of atrial fibrillation and increased incidence of thromboembolism in patients with hypertrophic cardiomyopathy. Jpn Circ J 59:329–336
8. Maron BJ, McKenna WJ, Danielson GK et al (2003) American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology foundation task force on clinical expert consensus documents and the European Society of Cardiology committee for practice guidelines. J Am Coll Cardiol 42:1687–1713
9. Christiaans I, van Engelen K, van Langen IM et al (2010) Risk stratification for sudden cardiac death in hypertrophic cardiomyopathy: systematic review of clinical risk markers. Europace 12:313–321

10. Maron BJ (2010) Contemporary insights and strategies for risk stratification and prevention of sudden death in hypertrophic cardiomyopathy. Circulation 121:445–456
11. Kubo T, Kitaoka H, Okawa M et al (2010) Hypertrophic cardiomyopathy in the elderly. Geriatr Gerontol Int 10:9–16
12. Oakley GD, McGarry K, Limb DG, Oakley CM (1979) Management of pregnancy in patients with hypertrophic cardiomyopathy. Br Med J 1:1749–1750
13. Siu SC, Sermer M, Colman JM, Alvarez AN, Mercier LA, Morton BC, Kells CM, Bergin ML, Kiess MC, Marcotte F, Taylor DA, Gordon EP, Spears JC, Tam JW, Amankwah KS, Smallhorn JF, Farine D, Sorensen S (2001) Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation 104:515–521
14. Autore C, Conte MR, Piccininno M, Bernabo P, Bonfiglio G, Bruzzi P, Spirito P (2002) Risk associated with pregnancy in hypertrophic cardiomyopathy. J Am Coll Cardiol 40:1864–1869
15. Avila WS, Rossi EG, Ramires JA, Grinberg M, Bortolotto MR, Zugaib M, da Luz PL (2003) Pregnancy in patients with heart disease: experience with 1,000 cases. Clin Cardiol 26:135–142
16. Thaman R, Varnava A, Hamid MS, Firoozi S, Sachdev B, Condon M, Gimeno JR, Murphy R, Elliott PM, McKenna WJ (2003) Pregnancy related complications in women with hypertrophic cardiomyopathy. Heart 89:752–756
17. Tanaka H, Kamiya C, Katsuragi S, Tanaka K, Miyoshi T, Tsuritani M, Yoshida M, Iwanaga N, Neki R, Yoshimatsu J, Ikeda T (2014) Cardiovascular events in pregnancy with hypertrophic cardiomyopathy. Circ J 78:2501–2506
18. McKenna WJ, Deanfield J, Faruqui A et al (1981) Prognosis in hypertrophic cardiomyopathy: role of age and clinical, electrocardiographic and hemodynamic features. Am J Cardiol 47:532–538
19. Nienaber CA, Hiller S, Spielmann RP et al (1990) Syncope in hypertrophic cardiomyopathy: multivariate analysis of prognostic determinants. J Am Coll Cardiol 15:948955
20. Maron BJ, Roberts WC, Epstein SE et al (1982) Sudden death in hypertrophic cardiomyopathy: a profile of 78 patients. Circulation 65:1388–1394
21. Geisterfer-Lowrence AAT, Kass S, Tanigawa G et al (1990) A molecular basis for familial hypertrophic cardiomyopathy: a β cardiac myosin heavy chain gene missense mutation. Cell 62:999–1006
22. Kimura A (2010) Molecular basis of hereditary cardiomyopathy: abnormalities in calcium sensitivity, stretch response, stress response and beyond. J Hum Genet 55:81–90
23. Landstrom AP, Ackerman MJ (2010) Mutation type is not clinically useful in predicting prognosis in hypertrophic cardiomyopathy. Circulation 122:2441–2450
24. Watkins H, Ashrafian H, Redwood C (2011) Inherited cardiomyopathy. N Engl J Med 364(17):364–356
25. Watkins H, McKenna WJ, Thierfelder L et al (1995) Mutations in the genes for cardiac troponin T and alpha-tropomyosin in hypertrophic cardiomyopathy. N Engl J Med 332:1058–1064
26. Anan R, Greve G, Thierfelder L et al (1994) Prognostic implications of novel beta cardiac myosin heavy chain gene mutations that cause familial hypertrophic cardiomyopathy. J Clin Invest 93:280–285
27. Ommen SR, Gersh BJ (2009) Sudden cardiac death risk in hypertrophic cardiomyopathy. Eur Heart J 30:25582559
28. Christiaans I, Birnie E, van Langen IM et al (2010) The yield of risk stratification for sudden cardiac death in hypertrophic cardiomyopathy myosin-binding protein C gene mutation carriers: focus on predictive screening. Eur Heart J 31:842–848
29. Ho CY (2010) Genetics and clinical destiny: improving care in hypertrophic cardiomyopathy. Circulation 122:24302440
30. Force T, Bonow RO, Houser SR et al (2010) Research priorities in hypertrophic cardiomyopathy. Report of a working group of the National Heart, Lung, and Blood Institute. Circulation 122:1130–1133
31. Turner GM, Oakley CM, Dixon HG (1968) Management of pregnancy complicated by hypertrophic obstructive cardiomyopathy. Br Med J 4:281–284

Peripartum Cardiomyopathy

11

Chizuko Aoki-Kamiya

Abstract

Peripartum cardiomyopathy (PPCM) is a specific cardiomyopathy in which heart failure develops during pregnancy or in the postpartum period in women without a history of heart disease, and reduced myocardial contraction is found on examination. The frequency of this condition is low in routine medical practice, but it should be included in differential diagnosis for pregnant and postpartum women who complain of dyspnea and excessive edema because it may lead to maternal death in severe cases. Advanced age, grand multipara, multiple conception, hypertensive disorders in pregnancy (HDP), and use of tocolytic agents are known risk factors. Especially, HDP is the strongest risk factor and complicates in about 40% of PPCM patients. A Japanese survey found that PPCM patients with HDP tended to have better long-term outcomes than those without. In contrast, PPCM patients with truncating variants associated with dilated cardiomyopathy (DCM) tended to have lower cardiac function in long-term than those without. Basic studies in animals and genetic analyses have recently been reported, and an association between vascular disorder such as HDP cardiomyopathy is currently attracting attention. Since "peripartum cardiomyopathy" is a diagnosis of exclusion, it indicates that PPCM is a group of heterogeneous conditions.

Keywords

Cardiomyopathy · Heart failure · Hypertensive disorders in pregnancy · Antiangiogenic factors

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11.1 Definition

Criteria proposed by Demakis et al. in 1971 [1] combined with specific values of reduction of left ventricular (LV) systolic function are often used for diagnosis of peripartum cardiomyopathy (PPCM), but there are no standard diagnostic criteria (Table 11.1) [2, 3]. LV ejection fraction (LVEF) <45% is frequently used as a criterion for LV systolic dysfunction. "The development of heart failure within 1 month before delivery" was originally included in the diagnostic criteria, since induction of heart failure by pregnancy-induced circulatory overload in cases with subclinical cardiac dysfunction before pregnancy cannot be ruled out in patients who develop heart failure before the last month of pregnancy [1]. However, in 2005, Elkayam et al. reported that cardiomyopathy developed earlier than 1 month before delivery in about 20% of patients who developed cardiomyopathy during pregnancy or the puerperal period and that the background, clinical findings at onset, and outcome of these patients were quite similar to those of patients meeting the diagnostic criteria [4]. These findings have prompted a movement to define the onset time of the disease as late pregnancy to include development earlier than 1 month before delivery.

Table 11.1 Definition/classification of peripartum cardiomyopathy [2, 3]

European Society of Cardiology on the classification of cardiomyopathies	A non-familial, non-genetic form of dilated cardiomyopathy associated with pregnancy
AHA Scientific on contemporary definitions and classifications of the cardiomyopathies	A rare and dilated acquired primary cardiomyopathy associated LV dysfunction and heart failure
Workshop held by the National Heart Lung and Blood Institute and the Office of Rare Diseases	The development of heart failure in the last month of pregnancy or within 5 months postpartum The absence of an identifiable cause of heart failure The absence of recognizable heart disease prior to the last month of pregnancy LV systolic dysfunction demonstrated by classical echocardiographic criteria. The latter may be characterized as an LV ejection fraction <45%, fractional shortening <30%, or both, with or without an LV end-diastolic dimension >2.7 cm/m^2 body surface area
Heart Failure Association of the European Society of Cardiology Working Group on PPCM 2010	PPCM is an idiopathic cardiomyopathy presenting with heart failure secondary to left ventricular systolic dysfunction towards the end of pregnancy or in the months following delivery, where no other cause of heart failure is found. It is a diagnosis of exclusion. The left ventricle may not be dilated, but the ejection fraction is nearly always reduced below 45%
The guideline of cardiomyopathy by the Japanese Circulation Society	The cardiac dysfunction, characterized by dilated and diffuse hypokinesis of LV like idiopathic dilated cardiomyopathy, among the women in late pregnancy and within several months after delivery

AHA American Heart Association, *LV* left ventricle, *PPCM* peripartum cardiomyopathy

There is no feature specific to PPCM, and the disease is diagnosed by excluding other diseases. When diseases to be differentiated, such as myocardial infarction and myocarditis, are excluded, and no other cause of cardiac dysfunction is observed, PPCM is finally diagnosed. However, it is difficult to differentiate PPCM from dilated cardiomyopathy (DCM) because there is no specific test for either disease and they may overlap, as described below. In this context, it is of note that a microRNA-146a has recently been detected specifically in patients with PPCM, not in normal pregnant controls or patients with DCM [5].

In Japanese nationwide survey of PPCM performed in 2009, 30% and 70% of patients were diagnosed during pregnancy and after delivery, respectively, and one-third were diagnosed within 1 week after delivery (Fig. 11.1) [6]. The chief complaint at the time of diagnosis was shortness of breath in 80%, cough in 37%, edema in 37%, malaise in 24%, palpitation in 20%, and weight gain in 16%. Since these symptoms are also frequent in healthy pregnant and parturient women, diagnosis is likely to be delayed. When pregnant and parturient women with the risk factors described below complain of shortness of breath, edema, and palpitation, it is important to consider PPCM. Brain natriuretic peptide (BNP) and its precursor, NT-Pro BNP, which are useful for screening of heart failure, increase in many patients. The mean BNP level at the time of diagnosis of heart failure in the nationwide survey was 1258 pg/mL (normal value <18 pg/mL), and only 4% of all patients had BNP <100 pg/mL. Therefore, these tests may be widely applicable for simple screening of heart failure even during and after pregnancy.

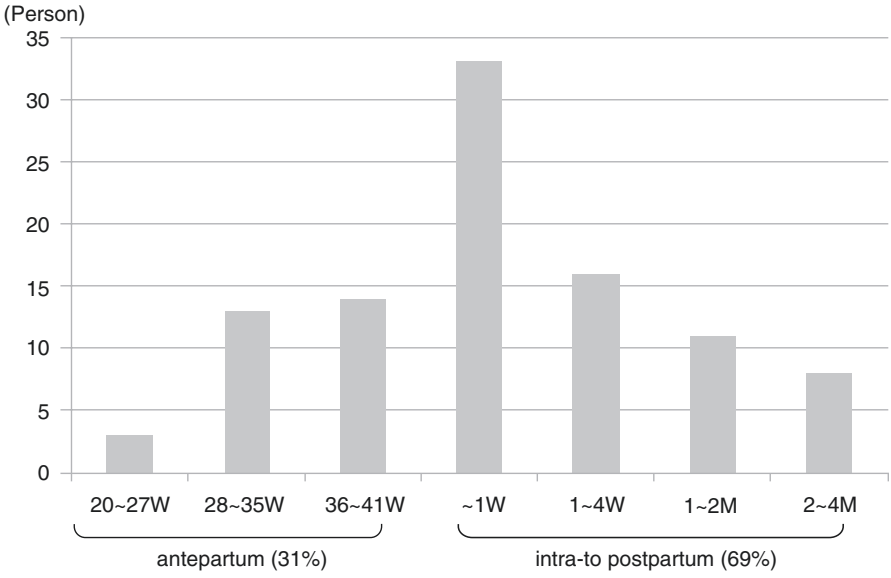

Fig. 11.1 Timing of diagnosis of PPCM in Japan [6]. *PPCM* peripartum cardiomyopathy

11.2 Incidence and Risk Factors

More than 50 patients/year are newly diagnosed as PPCM in Japan [6]. The incidence is 1 in 10,000–20,000 deliveries, which is lower than that of about 1 in 1000–3000 deliveries in the USA and also lower than reported rates in other countries. In addition to racial differences and women giving many births, lifestyle differences (such as fewer chronic hypertensive women at childbearing age) and the presence of undiagnosed cases may explain these results. The incidence has increased yearly in the USA with aging of pregnant women, improvement of reproductive technology, and an increase in the diagnosis rate. Similar tendencies are apparent in Japan, which suggests that the incidence may increase in the future.

Demakis et al. proposed multiple births, advanced age, multiple conceptions, preeclampsia and African race as risk factors [1]. Significantly higher frequency of use of tocolytic agents, concomitant chronic hypertension, and cigarette smoking may also be risk factors. The incidence has increased with aging in Japan (Fig. 11.2), and hypertensive disorders in pregnancy (HDP), use of tocolytic agents, and multiple conceptions are risk factors as well. International comparisons of patient background and clinical course are presented in Table 11.2 [6–11]. The complication rate with risk factors in Japan is comparable to those in the USA and Germany, which shows that the clinical features of PPCM are similar in Japan and Western

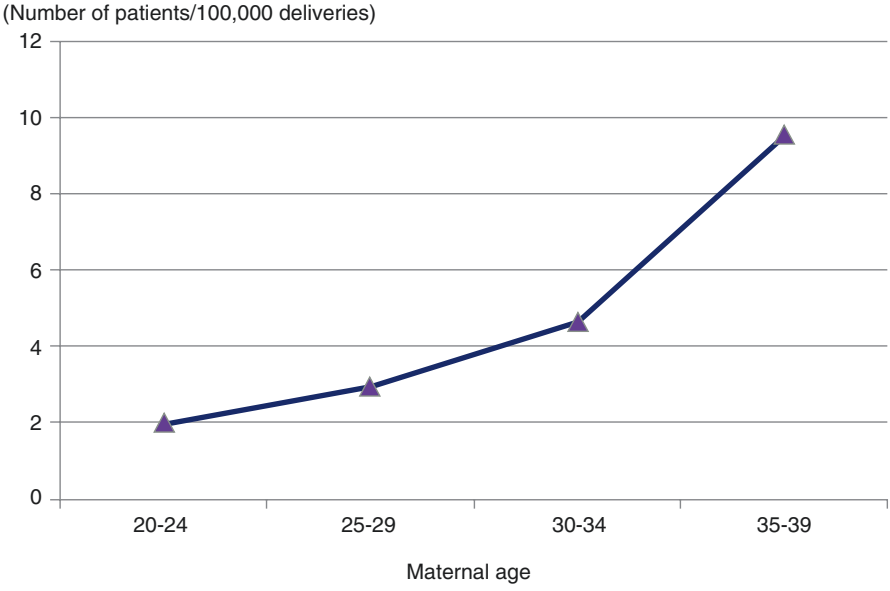

Fig. 11.2 Incidence of PPCM per 100,000 deliveries by age in Japan [6]. The number of deliveries in Japan in each age group were taken from national statistics published by the Ministry of Health, Labour and Welfare. *PPCM* peripartum cardiomyopathy

Table 11.2 The comparison of clinical pictures of PPCM among Japan, Germany, the USA, and South Africa [6–11]

	Japan	Germany	USA	South Africa
	$n = 102$	$n = 115$	$n = 100$	$n = 100$
Age (years)	32.7	34	30	31.6
Parity	1.7	2	2.2	3
Primiparas (%)	55	–	–	20
African descent (%)	0	–	30	100
Risk factors				
Hypertensive disorders in pregnancy (%)	42	45	45	2
Tocolytic therapy (%)	14	4	–	9
Twin pregnancy (%)	15	15	–	6
Mortality (%)	4	2	4	15

countries. The incidence is high in grand multiparas, but more than half of patients which are primiparas in Japan reflected on the declining birth rate.

11.3 Cause of Disease

There are various theories for the cause of PPCM, but this is still unclear. In addition to autoimmune reaction and viral infection theories, manifestation of an originally present pathology of DCM induced by cardiac overload associated with pregnancy and delivery has been proposed because the pathology is similar to that of DCM. However, since the incidence in pregnant and parturient women is higher than that of DCM in women in the same generation, the US NIH Workshop Group concluded that the pathology differs from that of DCM and that pregnancy is directly involved in development of the condition [12].

The key aspect of the etiology and pathogenesis is that PPCM is diagnosed by excluding other diseases. Therefore, it is a disease group with diverse backgrounds.

11.3.1 Antiangiogenic Factors

In the Japanese nationwide survey, the cardiac function recovered significantly higher in patients with HDP in the background [6]. It may indicate that PPCM with the background of HDP is one of the subsets of the disease. Vascular disorder is currently viewed as the main pathology of HDP. Involvement of antiangiogenic factors in PPCM has been suggested in an animal study and may be a common pathology in these diseases. The results of two basic studies suggesting an association between antiangiogenic factors and PPCM are discussed below.

11.3.1.1 Cleaved Prolactin Theory [13]

In 2007, Hilfiker-Kleiner et al. proposed a developmental mechanism for PPCM based on the observation that female mice with increased intracardiomyocyte oxidative stress develop cardiomyopathy and heart failure at a high rate during pregnancy and delivery. An increase in intracardiomyocyte oxidative stress promotes activity of a proteolytic enzyme, cathepsin D, which cleaves a lactogenic hormone, prolactin, in the circulation when the blood level increases in the perinatal period. Cleaved prolactin has antiangiogenic properties, such as inhibition of angiogenesis, suggesting its involvement in development of cardiomyopathy. Cardiomyopathy was inhibited when an anti-prolactin drug, bromocriptine, was administered before mice became pregnant and delivered. In addition, cleaved prolactin is present in serum of patients with PPCM, and cardiomyopathy can be prevented by bromocriptine in the next pregnancy in patients with a history of PPCM.

11.3.1.2 Angiogenesis Inhibition Theory [14]

In 2012, Patten et al. showed that hypertension and cardiomyopathy developed after several pregnancies and deliveries in mice in which PGC-1α, which is involved in angiogenesis by promoting secretion of vascular endothelial growth factor (VEGF), was knocked out specifically in heart muscle. Interestingly, cardiomyopathy was not reduced by VEGF administration in this mouse model, but the disease was inhibited by bromocriptine given in addition to VEGF. Thus, inhibition of angiogenesis by several factors, such as production of cleaved prolactin and reduction of VEGF, may induce PPCM.

11.3.2 Overlapping with DCM

In 2010, a gene mutation related to DCM was detected in patients with PPCM with a familial history of DCM [15, 16]. In latest recent genetic study conducted in the USA, Germany, and Japan, mutations of 43 genes related to DCM were screened in 172 patients with PPCM, and 26 (15%) were positive [17]. This rate was the same as that in a DCM cohort and significantly higher than that of 4.7% in a general cohort, and two-thirds of the patients had a titin gene mutation. In a US PPCM cohort study (the IPAC study), in which 11 patients with and 68 patients without titin gene aberrations were compared, quite a few patients with titin aberrations were complicated by HDP, although HDP was the strongest risk factor of PPCM. Moreover, recovery of cardiac function after 1 year was significantly lower in these patients. It is still controversy whether patients with a hereditary background related to DCM should be included in the definition of PPCM or not. As described in the section on diagnostic criteria, the disease is defined as “nonfamilial pregnancy-associated cardiomyopathy without a hereditary background of DCM” in the cardiomyopathy classification established by the European Society of Cardiology. However, many pregnant women with asymptomatic DCM diagnosed

before pregnancy complete pregnancy and delivery without complication. Therefore, a certain cardiac function-aggravating factor specific to PPCM may also be present in patients with a hereditary background [11].

The above findings indicate that patients can have different backgrounds, such as HDP and DCM, which indicates that PPCM is a group of heterogeneous diseases. At present, it is considered to be a disease group comprising vascular disorder, hereditary predisposition, and inflammation that occur alone or overlap. Studies using basic experiments have been initiated to explore the cause of the disease.

11.4 Treatment

PPCM is generally treated similarly to heart failure. For severe cases, intra-aortic balloon pumping (IABP) or percutaneous cardiopulmonary support (PCPS) is used, in addition to treatment with catecholamines in the acute phase. In the chronic phase, oral drugs such as ACE inhibitors, β blockers, and diuretics are administered, but cases that are resistant to treatment may require heart transplantation or result in death. Other than general treatment of heart failure, treatment with steroids, immunosuppressors, and high-dose γ-immunoglobulin therapy have been tried, but no clear treatment effect has been obtained. Recently, anti-prolactin therapy has been proposed as a novel treatment based on the theory that cleaved prolactin is a cause of the disease, as described above. In 2010, Sliwa et al. followed outcomes for 6 months in 20 patients with PPCM in South Africa who received standard treatment and bromocriptine ($n = 10$) or standard treatment alone ($n = 10$). The mortalities were 10% and 40%, respectively, and LVEFs of survivors after 6 months were 58% and 36%, respectively, showing large differences in outcomes [18]. In the muticenter trial with 63 PPCM patients whose LVEF <=35%, there was no significant difference in outcomes of 1-week and 8-week bromocriptine treatments [19].

11.5 Outcome

Demakis et al. initially reported that cardiac function recovered to normal in half of patients and that cardiac hypofunction persisted in the other half [20]. Thus, some cases can become severe and result in death or a need for heart transplantation. Subsequent studies in different countries and institutions have shown an LV function improvement rate of 7–50% and mortality of 4–80%. The marked variation among reports may have been due to the influence of race and differences in medical care. In a survey performed in 2009 in Japan, about 10% of patients died or required the left ventricular assist device during waiting for heart transplantation. Cardiac dysfunction persisted in about 30% of patients [6], while cardiac function recovered in normal range in about 60%. Treatment should be carefully performed, given that severe cases are fatal.

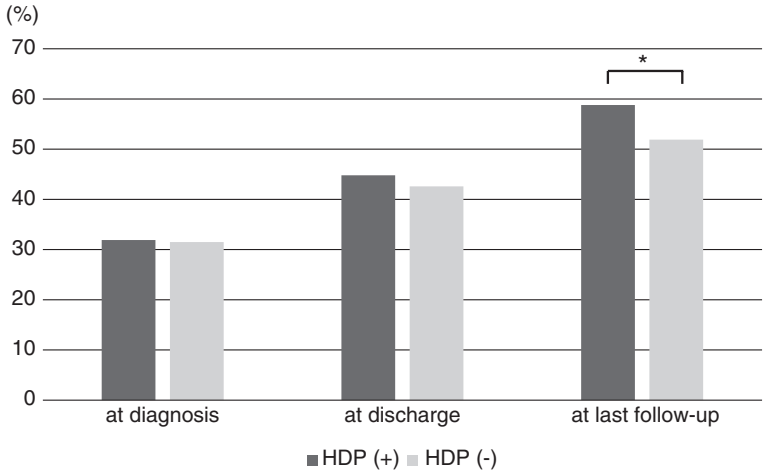

Fig. 11.3 Changes of LVEF in HDP (+) and HDP (−) groups. *LVDd*, *LVDs*, *%FS*, *LVEF* left ventricular ejection fraction, *HDP* hypertensive disorders in pregnancy. **p*-value < 0.05 for comparison of the HDP (+) and HDP (−) groups

The prognostic factors include LVEF on the first examination or 2 months after onset, LV end-diastolic dimension (LVDd), thrombus in the left ventricle, and race. A national survey in Japan showed that cardiac function is likely to recover in the chronic phase in patients with PPCM complicated with HDP (Fig. 11.3) [6], and a similar tendency was found in a national survey in Germany [7]. The cardiac function recovery rate is low in patients with a familial history of DCM and a related gene mutation [17, 21].

11.6 Typical Cases Presentation

PPCM is a heterogeneous disease group because it is diagnosed by exclusion of other diseases. Two typical cases with different backgrounds such as HDP and DCM are presented below.

11.6.1 A Case with HDP

Primipara with no past or familial medical history. Excessive edema and shortness of breath on exertion appeared at the 34th week of pregnancy. On prenatal checkup at the 37th week, blood pressure was 142/92 mmHg, and urinary protein was 3+. Preeclampsia was diagnosed, and the patient was admitted to hospital. On urinalysis after admission, urinary protein was 6 g/day, showing marked proteinuria, and +17 kg weight gain was noted compared with body weight before pregnancy. Orthopnea

appeared in the following week, and emergency Caesarean section was performed. After delivery, diuresis and reduction of body weight were favorable, but the resting heart rate (HR) exceeded 120 bpm 4 days after delivery, and cardiac dilatation was noted on chest radiography (Fig. 11.4a). The patient was then transferred to our hospital. At the time of transfer, NYHA class was IV, blood pressure was 126/88 mmHg, and BNP was markedly increased to 1581 pg/mL. On echocardiography, LVDd/LV end-systolic dimension (LVDd/Ds) was 57/54 mm, showing mild LV dilatation and severe hypokinesia; the left interventricular septum/posterior wall thickness (IVS/PW) was 9/8 mm, retaining the wall thickness; LVEF was 14%; and there was a small volume of pericardial effusion (Fig. 11.4b). There were no other specific findings, and the patient was diagnosed with PPCM. Internal medical treatment resulted in LVEF of 45% after 1 month. At 6 months, LVDd/Ds was 46/29 mm, IVS/PW 5/6 mm, and LVEF 60%, showing normalized cardiac function (Fig. 11.4c).

11.6.2 A Case with Family History of DCM

Primipara with no medical history, but her father died young from suspected cardiomyopathy. She had no subjective symptoms of the circulatory system or abnormalities in medical checkups before pregnancy. Excessive edema and shortness of breath on exertion appeared at the 32nd week of pregnancy. Cr was 1.4 at the 38th week, showing aggravation of renal function, and Caesarean section was performed. After delivery, severe cardiac dysfunction (LVEF 10%) was noted, and low cardiac output was considered to be the cause of aggravation of renal function. Treatment with catecholamines, hANP, and furosemide was initiated, but the response was weak. An IABP was inserted 3 days after delivery, and the patient was transferred to our hospital. At the time of transfer, she was NYHA class IV, and blood pressure was 110/68 mmHg. Marked pleural effusion and cardiac dilatation were noted on chest radiography (Fig. 11.5a), and BNP was 812 pg/mL. There was no increase in CK or antiviral antibody titer. On electrocardiography, only low voltage was detected, and no T-wave abnormality was noted. On echocardiography, LVDd/Ds was 55/50 mm, and LVEF was 12% (Fig. 11.5b). The patient was weaned from the IABP after 3 weeks. Cardiac function slowly improved, but LVEF was still 30% after 6 months, showing persistent cardiac dysfunction (Fig. 11.5c).

11.7 Recurrence Rate in a Subsequent Pregnancy

Since pregnancy and delivery are thought to be involved in development and progression of PPCM, repeated pregnancy is accompanied by a high risk in women with a history of the disease. In a review of reports on patients with this history who delivered a second child, the patients were divided into 98 with LVEF ≥50% (normalized cardiac function) and 93 with LVEF <50% (cardiac dysfunction) [22]. The recurrence rates were about 30% and 50%, respectively, and maternal death occurred in the cardiac hypofunction group (Table 11.3). This suggests that repeated

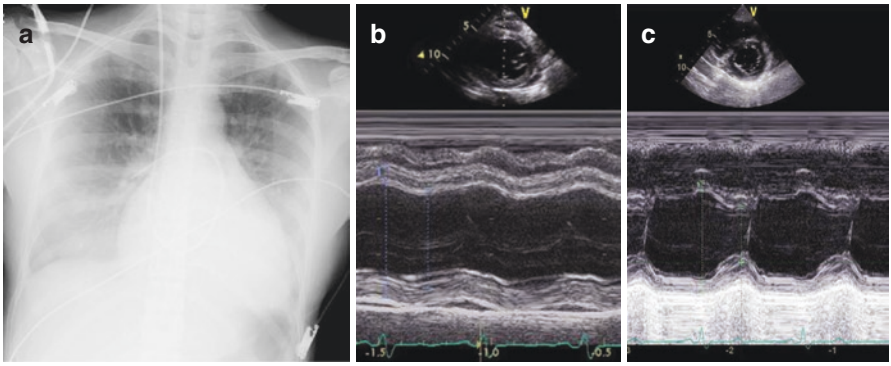

Fig. 11.4 A case with HDP. Chest radiography at the time of diagnosis (**a**): the cardiothoracic ratio was 66%, and pulmonary congestion was observed. Left parasternal-LV short axis M-mode echocardiography at the time of diagnosis (**b**), showing mild dilatation and marked reduction of systolic function of the left ventricle, and after 6 months (**c**), showing that LV systolic function had improved to the normal range. *HDP* hypertensive disorders in pregnancy, *LV* left ventricle

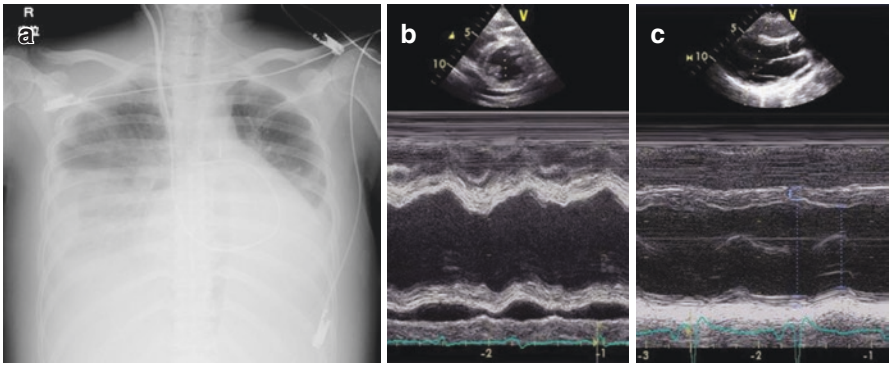

Fig. 11.5 A case with family history of DCM. Chest radiography at the time of diagnosis (**a**): massive pleural effusions and pulmonary congestion was observed. Left parasternal-LV short axis M-mode echocardiography at the time of diagnosis (**b**), showing mild dilatation and marked reduction of systolic function of the left ventricle, and left parasternal-LV long axis M-mode echocardiography after 6 months (**c**), showing that LV systolic dysfunction had not recovered. *HDP* hypertensive disorders in pregnancy, *LV* left ventricle, *DCM* dilated cardiomyopathy, *LV* left ventricle

pregnancy should be avoided in patients in whom cardiac dysfunction persists in the chronic phase after onset. Thus, "previous PPCM with any residual impairment of LV function" is a contraindicated pathology in the guidelines on pregnancy with concomitant cardiovascular disease established by the European Society of Cardiology [23]. In contrast, repeated pregnancy for patients in whom cardiac function recovered has become accepted on the premise that they fully understand the risk of recurrence.

Table 11.3 Outcome of subsequent pregnancies [22]

	Normal LV function before subsequent pregnancy[a] ($n = 98$)	Persistent LV dysfunction before subsequent pregnancy[b] ($n = 93$)
Deterioration of LV function	18/66 (27%)	40/84 (48%)
Symptoms of heart failure	20/63 (32%)	22/45 (49%)
Persistently decreased LVEF at follow-up	9/71 (13%)	36/93 (39%)
Death	0/63 (0%)	11/67 (16%)

LV left ventricular, *LVEF* left ventricular ejection fraction
[a]LVEF ≥ 50%
[b]LVEF < 50%

References

1. Demakis JG, Rahimtoola SH (1971) Peripartum cardiomyopathy. Circulation 44:964–968
2. Sliwa K, Hilfiker-Kleiner D, Petrie MC et al (2010) Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy. Eur J Heart Fail 12:767–778
3. Tomoike H, Izumi T, Imaizumi T et al (2016) Guidelines for management of dilated cardiomyopathy and secondary cardiomyopathy (JCS 2011). Circ J 80:753–774. http://www.j-circ.or.jp/form/kankoubutsu/guuideline_index.htm
4. Elkayam U, Akhter MW, Singh H et al (2005) Pregnancy-associated cardiomyopathy: clinical characteristics and a comparison between early and late presentation. Circulation 111(16):2050–2055
5. Halkein J, Tabruyn SP, Ricke-Hoch M et al (2013) MicroRNA-146a is a therapeutic target and biomarker for peripartum cardiomyopathy. J Clin Invest 123:2143–2154
6. Kamiya CA, Kitakaze M, Ishibashi-Ueda H et al (2011) Different characteristics of peripartum cardiomyopathy between patients complicated with and without hypertensive disorders. Results from the Japanese Nationwide survey of peripartum cardiomyopathy. Circ J 75:1975–1981
7. Haghikia A, Podewski E, Libhaber E et al (2013) Phenotyping and outcome on contemporary management in a German cohort of patients with peripartum cardiomyopathy. Basic Res Cardiol 108:366
8. McNamara DM, Elkayam U, Alharethi R, Damp J, Hsich E, Ewald G et al (2015) Clinical outcomes for peripartum cardiomyopathy in North America: results of the IPAC Study (Investigations of Pregnancy-Associated Cardiomyopathy). J Am Coll Cardiol 66:905–914
9. Sliwa K, Fett J, Elkayam U (2006) Peripartum cardiomyopathy. Lancet 368:687–693
10. Sliwa K, Forster O, Libhaber E, Fett JD, Sundstrom JB, Hilfiker-Kleiner D, Ansari AA (2006) Peripartum cardiomyopathy: inflammatory markers as predictors of outcome in 100 prospectively studied patients. Eur Heart J 27:441–446
11. Kamiya CA, Yoshimatsu J, Ikeda T (2016) Peripartum cardiomyopathy from a genetic perspective. Circ J 80:1684–1688
12. Pearson GD, Veille JC, Rahimtoola S et al (2000) Peripartum cardiomyopathy: National Heart, Lung, and Blood Institute and Office of Rare Diseases (National Institutes of Health) workshop recommendations and review. JAMA 283:1183–1188
13. Hilfiker-Kleiner D, Kaminski K, Podewski E et al (2007) A cathepsin D-cleaved 16 kDa form of prolactin mediates postpartum cardiomyopathy. Cell 128:589–600
14. Patten IS, Rana S, Shahul S et al (2012) Cardiac angiogenic imbalance leads to peripartum cardiomyopathy. Nature 485:333–338

15. Morales A et al (2010) Rare variant mutations in pregnancy-associated or peripartum cardiomyopathy. Criculation 121:2176–2182
16. van Spaendonck-Zwarts KY, van Tintelen JP, van Veldhuisen DJ et al (2010) Peripartum cardiomyopathy as a part of familial dilated cardiomyopathy. Circulation 121:2169–2175
17. Ware JS, Li J, Mazaika E et al (2016) Shared genetic predisposition in peripartum and dilated cardiomyopathies. N Engl J Med 374:233–241
18. Sliwa K, Blauwet L, Tibazarwa K et al (2010) Evaluation of bromocriptine in the treatment of acute severe peripartum cardiomyopathy: a proof-of-concept pilot study. Circulation 121:1465–1473
19. Arrigo M, Blet A, Mebazaa A (2017) Bromocriptine for the treatment of peripartum cardiomyopathy: welcome on BOARD. Eur Heart J 38(35):2680–2682
20. Demakis JG, Rahimtoola SH, Sutton GC et al (1971) Natural course of peripartum cardiomyopathy. Circulation 44:1053–1061
21. van Spaendonck-Zwarts KY, Posafalvi A, van den Berg MP et al (2014) Titin gene mutations are common in families with both peripartum cardiomyopathy and dilated cardiomyopathy. Eur Heart J 35:2165–2173
22. Elkayam U (2014) Risk of subsequent pregnancy in women with a history of peripartum cardiomyopathy. J Am Coll Cardiol 64:1629–1636
23. Regitz-Zagrosek V, Lundqvist CB, Borghi C et al (2011) ESC guidelines on the management of cardiovascular diseases during pregnancy. Eur Heart J 32:3147–3197

Pulmonary Arterial Hypertension

12

Shinji Katsuragi and Tomoaki Ikeda

Abstract

Pulmonary arterial hypertension (PAH) is a complex disorder in which pulmonary artery (PA) obstruction leads to elevated PA resistance and right ventricular (RV) failure. Elevation of the pulmonary arterial blood pressure (PABP) is correlated with progressive damage to the pulmonary artery. Before development of surgery for ventricular septal defect (VSD), atrial septal defect (ASD), and patent ductus arteriosus (PDA), most patients died around the age 40, with right-sided cardiac failure being the main cause of death. Deterioration in pregnancy is reported to occur in the second or third trimester and in the postpartum period. Sudden hemodynamic instability is a common cause of death. The risk of cardiac failure during and after pregnancy increases, and sudden cardiac arrest may occur during Cesarean section or soon after birth. The rate of maternal death in pregnancies complicated by PAH is variably reported to be 20–60%. Predictors of cardiac failure during pregnancy are elevated PABP, elevated brain natriuretic peptide (BNP), and elevated RV size. Current PAH-specific therapies have affected survival in nonpregnant PAH patients, and it is important to accumulate data from multiple PAH centers. Prostacyclins became available for PAH treatment in 1996 to the United States and Europe and in 1999 in Japan. Therefore, in this chapter, we classify studies on this condition temporally into pre- and post-PAH therapeutic eras.

Keywords

Pregnancy · Pulmonary arterial hypertension · Pulmonary vascular disease Right ventricular failure

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12.1 Definition and Mechanisms

Pulmonary arterial hypertension (PAH) is defined as an increase in mean pulmonary arterial blood pressure (PABP) to ≥25 mmHg at rest, as assessed by right heart catheterization [1].

There have been reported four mechanisms of PAH [2]: (1) an increase in pulmonary blood flow (congenital heart disease with left to right shunt); (2) a decrease in the functional pulmonary vascular bed (hypoxic pulmonary vasoconstriction, chronic exposure to high altitude, sleep-disordered breathing, interstitial lung disease); (3) a decrease in the organic pulmonary vascular bed (chronic obstructive pulmonary disease, PAH (Fig. 12.1 left), chronic thromboembolic pulmonary hypertension); and (4) an increase in pulmonary vein pressure (pulmonary veno-occlusive disease, left ventricular (LV) failure).

12.2 Pathophysiology of PAH and Pregnancy

PAH occasionally occurs in women aged 20–30 years old in central childbearing age, and most mild cases are asymptomatic in the early stage, even though PABP is elevated.

During healthy pregnancy, peripheral resistance decreases by 16 weeks of gestation to permit increased uterine blood flow; however, in PAH, stenosis of the internal cavity is observed due to hypertrophy of arterial media caused by proliferation of pulmonary arterial smooth muscle cells (Fig. 12.1). In a normal pregnancy, the total blood volume increases by 40–50% by the end of the second trimester, but a decrease in the organic pulmonary vascular bed makes this impossible. Therefore, PAH patients sometimes become symptomatic during pregnancy;

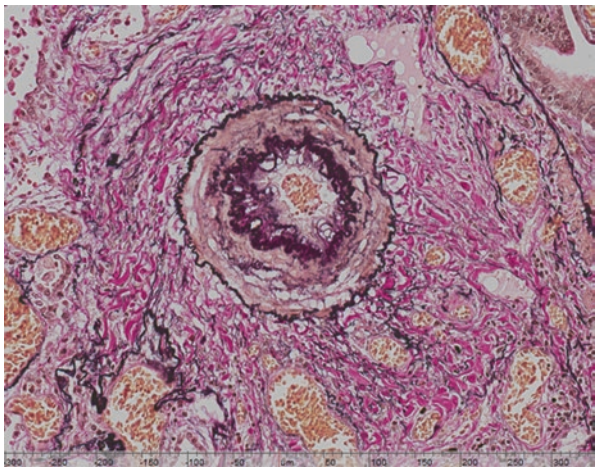

Fig. 12.1 Hypertrophy of arterial media by proliferation of the pulmonary arterial smooth muscle cells. Hypertrophy of arterial media occurs due to proliferation of pulmonary arterial smooth muscle cells, and this leads to stenosis of the internal cavity and decreased organic pulmonary vascular bed. Reprinted with permission from Dr. Hatsue Ishibashi-Ueda (National Cerebral and Cardiovascular Center, Japan)

PAH patients have exertional dyspnea, cough, and fatigue during pregnancy, and right heart failure, edema, ascites, and faintness with continuation of pregnancy persist. During pregnancy, most women have exertional fatigue and palpitation, and so these symptoms may be overlooked. At the time of consultation with a cardiologist, the disease has progressed, and many patients are already in NYHA class III or IV.

12.3 Pregnancy Outcomes

In 1996, epoprostenol was approved for treatment of PAH in the United States. Since then, prognosis of PAH patients had dramatically changed. Here, pregnancy outcomes are analyzed and compared before and after introducing pulmonary vasodilator therapy.

12.3.1 Experience of Severe PAH Cases in Pregnancy

We experienced three severe cases of idiopathic PAH (IPAH) in patients with maternal ages of 30, 38, and 20 years old. All were transferred to our hospital because of exacerbated exertional fatigue, dyspnea, and pretibial edema at 25–30 weeks gestational age. On admission, PaO_2 levels were 75, 66, and 86 mmHg, and PABPs were 72/30, 61/31, and 82/42 mmHg, respectively. NYHA classes were IV, IV, and III at the time of transfer to our hospital. Delivery by Cesarean section was performed at 32, 28, and 32 weeks of gestation under general anesthesia with continuous Swan-Ganz catheter and systemic blood pressure (via a radial arterial line) monitoring. Percutaneous cardiopulmonary support was ready for use in an emergency in each case. In the first case (in 1985), maternal death occurred intraoperatively. Emergency Cesarean section had been planned due to an abnormal fetal heart rate pattern, but the mother died of hypotension soon after intubation, despite attempts at resuscitation. In the other two cases (in 2000 and 2003), the women survived to leave hospital. We attribute these outcomes to improved management using pulmonary vasodilators such as epoprostenol IV therapy.

12.3.2 Pregnancy Outcomes in the Pre-PAH Therapeutic Era

In a review of the literature between January 1978 and December 1996, Weiss et al. [12] identified 73 patients with Eisenmenger's syndrome, 27 with IPAH (primary PAH), and 25 with PAH associated with other conditions (secondary PAH). All patients except for one delivered at 32 weeks or later. Pulmonary hypertensive crisis after oxytocin use occurred in one patient. Maternal mortality was 36% in Eisenmenger's syndrome, 30% in IPAH, and 56% in associated PAH. Except for three, all fatalities occurred within 35 days after delivery. Late maternal death several months postpartum occurred in three patients with Eisenmenger's syndrome.

The causes of death were pulmonary hypertensive crisis with therapy-resistant heart failure ($n = 13$), sudden death ($n = 7$), autopsy-confirmed pulmonary thromboembolism ($n = 3$), cerebral thromboembolism ($n = 1$), and rupture and dissection of the PA ($n = 1$). Twenty-two neonates (weight, 2372 ± 640 g) survived. One stillbirth and two neonatal deaths due to congenital anomalies resulted in a fetal/neonatal mortality rate of 12% (95% CI, 3–31%). These data suggest that pregnancy in the preprostacyclin era was associated with extremely high maternal and fetal morbidity and mortality.

12.3.3 Pregnancy Outcomes Overlapping the Pre- and Post-PAH Therapeutic Eras

Mortality and morbidity in pregnant patients with PAH improved somewhat over the next few years but remained high. Bonnin et al. [3] reviewed 15 pregnancies in 14 women from 1992 to 2002. The overall mortality was 36% (5 of 14 patients). In this series, three cases had early deterioration at weeks 12, 20, and 24 of gestation, and five other cases had deterioration during the third trimester.

A study of 42 pregnant women with PAH in Japan was performed retrospectively from January 1982 to December 2007 [4]. Patients were divided into those with mild PAH (systolic PAP 30–50 mmHg on echocardiography or mPAP 25–40 mmHg by catheterization, $n = 14$) and severe PAH (systolic PAP ≥50 mmHg on echocardiography or mPAP ≥40 mmHg by catheterization, $n = 28$). The cohort included mostly patients with IPAH or congenital heart disease-associated PAH. All patients with severe PAH before pregnancy had evidence of worsening PABP in their last trimester of pregnancy, while most of those with mild PAH had a mild or no increase in PABP, although this latter group was assessed only by noninvasive methods. Patients with mild PAH delivered mostly at term, whereas those with severe PAH had earlier deliveries. The NYHA functional class worsened in all but two patients as pregnancy progressed. There was one death immediately after intubation for delivery.

Bédard et al. conducted a comparative analysis of articles published between 1997 and 2007. The overall mortality was 25% [5]. Parturients who received general anesthesia were 4 times more likely to die than those receiving regional anesthesia. Most deaths (78%) occurred within 1 month postpartum (15 deaths postpartum vs. 3 during pregnancy). Neonatal/fetal deaths occurred in 10%, 7%, and 13% of patients with IPAH, congenital disease-associated PAH, and conditions with associated PAH, respectively.

12.3.4 Pregnancy Outcomes in the PAH Therapeutic Era

Over the past decade, there have been several reports of patients with PAH successfully managed during pregnancy, suggesting an improved outcome with current therapies [6]. In a retrospective series of 18 pregnant patients with PAH (50% with

congenital heart disease) treated between 1999 and 2009 at five US medical centers [7], 6 underwent termination at a mean gestational age of 13 ± 1 weeks, with no maternal deaths or complications, and 12 elected to continue pregnancy. Nine of these patients (75%) received PAH-specific therapy at the time of delivery, consisting of sildenafil, IV prostanoids, or combination therapy. All parturients underwent Cesarean section at 34 weeks. There was one in-hospital death and one additional death 2 months postpartum, giving a maternal mortality rate of 16.7%.

In a study in China, a retrospective review was performed for 30 consecutive parturients with PAH hospitalized at Peking Union Medical College Hospital from January 1999 to December 2008 [8]. Eight had IPAH, seven had congenital heart disease-associated PAH, ten had rheumatic heart disease-associated PAH, and five had PAH due to other etiologies. PAH-specific therapy was only used in two patients with congenital heart disease-associated PAH. The maternal mortality rate was 17%, but patients with Eisenmenger's syndrome had 50% mortality. There were 4 fetal/neonatal deaths (13%) and 16 infants were born preterm. All 26 live-born infants survived.

In 2012, Rosengarten et al. [9] reported their recent experience of nine pregnancies in seven patients with PAH for whom a careful multidisciplinary approach was implemented. All but one patient were treated with IV prostacyclins, and all underwent planned Cesarean sections at term. Two patients died within 2 weeks after delivery (22% mortality), and there were no fetal deaths.

In a prospective study in 13 PAH centers in Europe, the United States, and Australia, Jaïs et al. [10] reported data and 3-year outcomes from 26 pregnancies between 2007 and 2010. During pregnancy, the patients were regularly seen at their centers, usually at 2- to 4-week intervals. Only one center in France performed right heart catheterization as part of their regular assessment during pregnancy. A total of 16 pregnancies (62%) were considered successful, defined as survival of the mother and the baby without complications. Six patients underwent induced abortion, and two had a spontaneous abortion, both of whom died. Three women died in the early postpartum period as a result of right heart failure, whereas one required urgent heart-lung transplantation. The outcomes of pregnancies were better in patients with lower PVR (500 ± 352 dyn·s/cm^5), whereas patients with a very high PVR (1667 ± 209 dyn·s/cm^5) died or required transplantation. Of note, 8 (50%) of the 16 women who had successful pregnancies were so-called vasodilator responders and had nearly normal baseline hemodynamic parameters with calcium channel blocker therapy. The other women with successful pregnancies were non-responders to calcium channel blockers, but most had well-controlled PAH while receiving PAH-specific therapy. Maternal outcomes during the year after delivery were analyzed for the 16 successful pregnancies. Two mothers (13%) had clinical deterioration requiring intensification of PAH therapy. Neither was a long-term responder to calcium channel blockers.

The UK experience is reported in two papers. In the first report, Kiely et al. [11] analyzed management of ten pregnancies in nine women who chose to continue with their pregnancies between 2002 and 2009 in a specialized PAH center. All were treated with 4–7 doses of nebulized iloprost per day, with two patients being

transitioned to IV prostacyclin and three additionally receiving sildenafil. Nine patients underwent planned Cesarean section. All women received regional anesthesia and were monitored during the peripartum period in a critical care setting. All survived the pregnancy and postpartum period, and all infants were free from congenital abnormalities. One woman died 4 weeks after delivery, following patient-initiated discontinuation of therapy. Long-term follow-up in the other patients was a median of 3.2 years (range, 0.8–6.5 years). The second UK report describes the outcome of 12 pregnancies in 9 women with PAH between 1995 and 2010 at one center [12]. .All women delivered by Cesarean section (seven elective and two emergency deliveries) under general anesthesia, except for one emergency and one elective Cesarean performed under regional block. There were two maternal deaths (in 1995 and 1998): one related to preeclampsia and one to arrhythmia. Maternal morbidity included postpartum hemorrhage (five cases) and one post-Cesarean evacuation of a wound hematoma. There were nine live births, three first-trimester miscarriages, and no perinatal deaths.

A very recent prospective international registry including centers from the United States and Europe reported on 26 pregnant patients with PAH (17 with IPAH, 9 with associated PAH). Six chose elective abortion, 16 delivered a healthy baby and survived without transplantation, and 4 died or underwent urgent transplantation [10]. Of the 16 patients who successfully delivered, 2 had clinical deterioration requiring intensification of PAH therapy.

Taken together, these data suggest that outcomes of pregnant patients with PAH have improved with the availability of new therapies, advances in surgical and perioperative management, and use of a team-based, multidisciplinary approach. However, despite the availability of new drugs and technologies, fetal and maternal morbidity and mortality remain high.

12.3.5 A Recent Case of Maternal Death in Japan

The Japanese maternal death registration system was started in 2010. All maternal death cases are submitted to the Japan Association of Obstetricians and Gynecologists (JAOG) for analysis. From 2010 to 2015, there were 266 maternal deaths, including 28 due to cardiovascular diseases, with 1 due to PAH. This case was a patient aged 32 years old, one gravida one para. Her previous pregnancy course had been normal. The current pregnancy course was also normal. At 37 weeks of gestation, she was transferred to a tertiary center because of low SpO_2, sinus tachycardia, and right heart strain in ECG, after feeling mild dyspnea and palpitation for 1 week. She had ruptured membranes and was in labor. SpO_2 was 93%, BP 109/81, HR 114/min, BGA pH 7.452, CO_2 23.3, O_2 62, HCO_3^- 16 BE-6.1. A dilated right pulmonary artery was detected in X-ray; ECG showed sinus tachycardia of 145 bpm, right axis deviation; the RV and right atrium were severely enlarged (Fig. 12.2a); the septum was pressed; and the LV had a D shape (Fig. 12.2b). Contrast CT excluded pulmonary thromboembolism. Annular dilatation of the tricuspid valve was observed and ΔPG of TR was 83 mmHg. Severe PAH was suspected. A cardiologist explained to

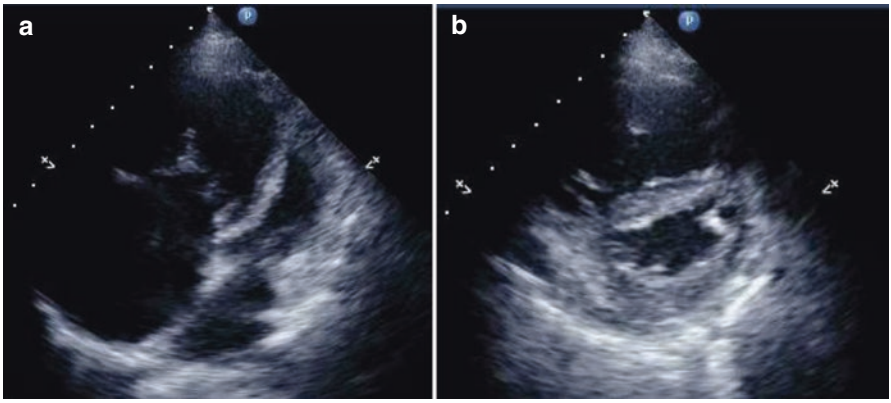

Fig. 12.2 Echocardiographic images of severe PAH. Echocardiographic images of severe PAH (TRPG 83 mmHg) at 34 weeks of gestation. The patient died after Cesarean section. The right heart was severely enlarged (**a**), and the septum was pressed, with the LV having a D shape (**b**)

the patient that she had severe IPAH. After Cesarean section, she needed 10 L/min O_2 and SpO_2 was 95%. The postpartum course was managed on bedrest in the ICU, with ECG, SpO_2, and radial artery line monitoring. On postpartum 1–4 days, heart rate was 100–110/min, nasal O_2 5/L was continued, and echocardiography on postpartum day 3 showed a D-shaped small LD. The patient showed cough and gallop rhythm, and SpO_2 was unstable. Blood pressure decreased and DOB was started, a small amount of volume load led to a decrease of SpO_2, and urinary output decreased to 30 ml/h. On day 5 she suddenly showed tetraplegia and paroxysmal tonic upgaze. An ECG showed pulseless electrical activity. She died after 1 h of resuscitation attempt. In the committee review, hypoxic shock due to increased PABP was determined to be the cause of death, and the death was judged to have been unavoidable.

12.3.6 Three Factors Decreasing Maternal Death (1995–2010)

Although 70% of maternal deaths reported in the literature occur postpartum, there were no such deaths in the series in Japan [4] and no deterioration of NYHA class postpartum. These results were attributed to three factors [4]. The first was early termination of pregnancy around 30 weeks of gestation in severe cases. Improvement of treatment in the NICU facilitated this decision, since all preterm infants survived without neurological disorders, despite weighing only 1000–1500 g with prematurity in most organs. The second factor was introduction of new drugs against PAH, including beraprost, sildenafil, and epoprostenol; and the third was improvement of anesthetic management. When PABP became higher than systemic blood pressure (SBP) during Cesarean section, especially after removal of the placenta, anesthesiologists were ready to reduce the blood volume by 100 ml in a few minutes from a Swan-Ganz catheter and use neosynesin 0.2 mg IV to raise SBP.

12.4 Pregnancy Management

Recommendations for pregnancy management for patients with PAH, separated by trimester and delivery, are based in part on the European Society of Cardiology guidelines on pregnancy in cardiovascular disease [13]. Because of the excessive risk to the mother and fetus in patients with PAH, termination (therapeutic abortion) should be offered regardless of the WHO class [14]. The first trimester is the safest time for elective termination; however, in a patient with PAH, termination carries a greater risk than in the general population and should be performed in a specialized center [13, 15]. Uterine dilatation and evacuation is the safest procedure [16]. If surgical evacuation is not feasible, medical abortion using prostaglandin E1 or E2 or misoprostol, a synthetic prostaglandin that is structurally related to prostaglandin E1, can be used to evacuate the uterus [16].

Management should be provided by a multidisciplinary team in a center with experience with treatment of pregnant patients with PAH. At a minimum, the team should include a PAH specialist, a cardiologist, an obstetrician, an anesthetist specialized in managing high-risk pregnancies, and a neonatologist [11, 13–15]. Pharmacists, intensivists, and social workers are also frequently needed. In addition, in a case with associated forms of PAH, specialists in the underlying disease should be involved. A plan for patient-specific multidisciplinary management should be put in place [11].

12.4.1 First Trimester

During the first trimester, the volume changes associated with pregnancy are less pronounced than those in future trimesters; thus, edema and swelling symptoms should trigger an evaluation of PAH status. Even in the absence of symptoms, regular assessment of PAH status is advisable using physical examination, echocardiography, brain natriuretic peptide, and 6-min-walk test at regular intervals during the trimester.

12.4.2 Second and Third Trimesters

Circulating blood volume gradually increases by about 50% up to around 30 weeks of gestation and then plateaus [17]. In severe cases, this early rise leads to decompensation and the need for delivery. The signs of decompensation are dyspnea, exertional fatigue, and pretibial edema. Patients may show signs and symptoms of right heart failure, arrhythmia, or angina (resulting from RV ischemia) if pregnancy is allowed to continue. Echocardiography frequency may be increased to every 2 weeks if concerns of worsening right heart function arise during this trimester. Patients with right heart failure symptoms require hospitalization, and an enlarged RV may be observed (Fig. 12.2). Standard therapies are diuretics and oxygen therapy. To avoid caval vein compression, the patient should be advised to lie in the lateral position.

The main concerns in the third trimester are preparation for delivery and ensuring continued safety of the mother and fetus. In this trimester, echocardiograms are recommended every 1–2 weeks to monitor the cardiac status and adjust PAH medications. As in the second trimester, important nonpharmacologic therapy involves limiting sodium and excessive fluid intake during pregnancy [18].

12.5 Delivery Management

The optimal timing of planned elective delivery in women with PAH is uncertain and involves an assessment of the maternal risk of continuing pregnancy and the risk of neonatal preterm delivery. In stable women, planned delivery around weeks 34–36 is recommended, with earlier delivery if there is evidence of symptomatic decline.

The mode of delivery should be carefully selected in a pregnant patient with PAH because this may influence the outcome. Cesarean section is the preferred mode of delivery [13]. Although vaginal delivery is usually associated with fewer bleeding complications and infections in the healthy population [19], the associated hemodynamic and physiological changes may be detrimental to a mother with PAH.

12.5.1 Vaginal Delivery

This mode of delivery is usually selected in patients with mild PAH but should be avoided in those with severe PAH because it has many disadvantages. First, vaginal delivery is associated with frequent use of the Valsalva maneuver, which increases intrathoracic pressure and thus decreases venous return. Second, labor-induced vasovagal responses can decrease venous return and lead to cardiopulmonary collapse. Third, the pain of childbirth may lead to sympathetic nervous system stimulation. As a result, there may be an increase in heart rate and increases in systemic and pulmonary vascular tone, with resultant hemodynamic instability. Labor-induced acidosis, hypercapnea, or hypoxia may further contribute to increases in PABP. Finally, agents used to induce labor may precipitate clinical deterioration. Low-dose oxytocin should be used with caution to induce labor, since it can increase PVR. If vaginal delivery is chosen, effective analgesia is imperative. Nitrous oxide should be avoided because of its potential to vasoconstrict the pulmonary vasculature [20], and epidural analgesia should be considered.

12.5.2 Cesarean Section

Cesarean section is the preferred mode of delivery and should be used unless unavailable or in an emergency [3, 11]. Cesarean section bypasses the hemodynamic complications associated with labor and autotransfusion associated with vaginal contractions. Elective Cesarean section avoids labor and allows for careful,

multidisciplinary planning and preparation of anesthesia, optimization of hemodynamics, and development of contingency plans. Moreover, Cesarean section does not appear to have a negative effect on outcomes [14]. The choice of anesthesia is important when Cesarean section is being considered and should be preplanned during early multidisciplinary meetings with the anesthesiologist, who should be aware of the hemodynamic changes associated with PAH (often an obstetric or cardiac anesthesiologist), and with an experienced maternal-fetal medicine specialist. The aim of the anesthesiologist is to achieve an optimum balance between anesthesia and side effects. Most obstetric units prefer regional anesthesia to general anesthesia for this procedure. This reduces risks associated with general anesthesia (e.g., endotracheal intubation and positive-pressure ventilation, which may increase PVR and RV afterload). However, a regional approach is not always possible, and plans should be made for general anesthesia if necessary.

12.5.3 Monitoring and General Considerations During Delivery

During labor and delivery, continuous monitoring of the electrocardiogram and pulse oximetry should be performed [13]. PA catheterization and monitoring of central venous pressure and intra-arterial blood pressure may be of benefit in selected cases, but there is no consensus regarding their routine use during delivery [5]. Close attention should be paid to avoid conditions that may lead to PA vasoconstriction and worsening RV function; these include hypoxia, hypercarbia, and acidosis. Anxiety- and pain-induced catecholamine release may negatively affect hemodynamics; the use of different anesthetic methods is discussed in detail below. To optimize oxygen delivery as much as possible, significant anemia should be corrected. The patient should be as euvolemic as possible, and major fluid shifts must be avoided as much as possible. Intravenous prostacyclins should be readily available. Individualized management plans for each patient should be discussed and updated before delivery.

12.6 Anesthesia in Pregnant Patients with PAH

12.6.1 General Anesthesia

General anesthesia depresses cardiac contractility, increases PVR via positive-pressure ventilation, and increases PAP during laryngoscopy and intubation [21, 22]. Bédard et al. [5] suggest that parturients who receive general anesthesia were more likely to die than those receiving regional anesthesia. However, caution is needed when interpreting these results because there may be a selection bias toward a sicker parturient receiving general anesthesia. If general anesthesia is required, the patient should be ventilated at the lowest airway pressure and tidal volume possible.

12.6.2 Epidural or Combined Spinal-Epidural Anesthesia

Epidural anesthesia with incremental doses has commonly been considered to be the best approach to regional anesthesia. However, with the advent of modern equipment and techniques, low-dose combined spinal-epidural anesthesia is increasingly used because it provides a denser perineal sensory block than epidural anesthesia alone, with little additional risk of hypotension [23].

Single-dose spinal anesthesia should be avoided in this patient population because of the risk of a rapid rise in block height that may cause uncontrollable hemodynamic instability as sympathetic block rises and systemic hypotension occurs [3].

12.7 Postpartum Complications: Faintness, Heart Failure, Thrombosis

In the hours and days after childbirth, blood volume is increased by autotransfusion of blood from the contracting uterus and by shifting of peripheral edema from the extravascular compartment into the systemic vasculature. In healthy subjects, these physiological changes are normally well tolerated, but in the presence of severe pulmonary vascular disease, hemodynamic instability may develop, leading to cardiorespiratory failure and/or sudden death [7, 13]. Parturition and the first postpartum week are particularly vulnerable periods for patients with PAH [7, 10]. Two systematic literature reviews have described the outcomes of pregnancy in women with PAH, covering a total of almost 30 years and comprising 198 pregnancies. The mortality of women with Eisenmenger's syndrome ($N = 102$) was 36% in the first review (1978–1996) [10] and 28% in the second review (1997–2007) [5]. Most of these women died in the first month after delivery, and the main causes of death were heart failure and sudden death, while pulmonary thromboembolism was another frequent cause. In women with IPAH ($N = 56$), mortality was 30% in the first [10] and 17% in the second [5] review. Similarly, nearly all fatalities in these patients occurred early in the postpartum period, and death was mainly due to heart failure, followed by sudden death and thromboembolism. Thus, the immediate postpartum period is a critical period for acute decompensation in patients with PAH. Patients should be closely monitored for several days postpartum, and monitoring in an intensive care unit in the first few days after delivery is recommended. Vagal reactions and syncope can have catastrophic consequences in patients with PAH, independent of pregnancy, because they may be associated with a profound drop in CO [24]. Vasovagal syncope is characterized by a temporary reduction of blood flow to the brain that is caused by sudden hypotension, change in heart rate, and change in blood volume or distribution [25]. The vasodilatory state in pregnant women makes them generally more prone to vasovagal syncope than nonpregnant women [26]. Patients with PAH are also more prone to syncope than healthy individuals [24], and the

combination of pregnancy and PAH creates a "perfect storm," generating a condition where vasovagal syncope is more prevalent and its consequences are particularly dangerous.

12.8 PAH-Directed Therapy in Pregnancy

Patients may present for the first time in pregnancy with PAH, or women with known PAH may plan pregnancy despite counseling on the high risk of maternal death. PAH patients may also accidentally become pregnant. If the woman chooses to continue pregnancy, there is emerging literature on the use of specific PAH therapies in pregnancy [6, 7, 11, 14, 27, 28]. Three classes of drugs are currently available for PAH treatment. Calcium channel blockers can also be used when appropriate.

12.8.1 Prostaglandins

Prostaglandins are potent pulmonary vasodilators that may also enhance RV function [29, 30]. Current parenteral prostaglandins (epoprostenol, treprostinil, and iloprost) are not known to be teratogenic (Table 12.1) and are listed as pregnancy category B (epoprostenol and treprostinil) or C (iloprost). Thus, they may be continued in patients who are taking these drugs before pregnancy, if physicians and patients agree that the benefits outweigh the relatively unknown risks. However, use of prostaglandins pre-pregnancy may be an indicator of more severe disease. In addition to the usual indications to begin prostaglandin therapy, such as WHO FC III or IV symptoms and reduced RV function [31–33], other considerations in pregnancy may compel therapy with parenteral prostaglandins. Examples are worsening symptoms or deteriorating RV function despite therapy with phosphodiesterase inhibitors and non-parenteral prostanoids. It should be recognized that maternal mortality may still be significant, even with parenteral prostanoids [9]. In many centers, IV prostanoids are managed exclusively by a PAH specialist, and this includes accompanying the patient to the operating room. In general, parenteral prostaglandins are recommended for pregnant patients with PAH in WHO FC IV or if there is evidence of severe RV impairment. Inhaled iloprost or treprostinil may be used in patients with less severe symptoms, and safe and successful use of these drugs in pregnancy has been reported [11, 27]. However, in a patient with deterioration while receiving inhaled prostaglandin therapy, rapid conversion to parenteral forms (some publications have advocated IV epoprostenol) [34] should be considered. If there is no rapid clinical improvement, immediate delivery should be considered because of the high risk of maternal death. In addition, inhaled epoprostenol or nitric oxide [35] has been administered to acutely ill patients as a bridge to initiation of parenteral treatment.

Table 12.1 FDA-assigned risk category for PAH medications

Drug	Pregnancy risk category
Epoprostenol	B
Treprostinil	B
Sildenafil	B
Tadarafil	B
Nitric oxide	C
Iloprost	C
Bosentan	X
Ambrisentan	X
Macitentan	X
Riociguat	X

FDA US Food and Drug Administration, *PAH* pulmonary arterial hypertension, *B* animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate, well-controlled studies in pregnant women, *C* animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate, well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks, *X* studies in animals or humans have demonstrated fetal abnormalities, and/or there is positive evidence of human fetal risk

12.8.2 Phosphodiesterase-5 Inhibitors

Sildenafil and tadalafil are both pregnancy category B drugs (Table 12.1). There are several reports of successful pregnancies managed with sildenafil alone or in combination with a prostaglandin [2, 7, 10, 12, 36]. Use of tadalafil in pregnancy has not been reported. In a larger case series of successful pregnancies, sildenafil was generally used in combination with a prostaglandin [7, 11, 37]. There is no published experience with tadalafil, and, thus, there is a preference for sildenafil in use of phosphodiesterase-5 inhibitors in pregnancy. However, this use should be restricted to combination therapy with a prostaglandin or, if used as monotherapy, restricted to patients who have normal RV function and near-normal pulmonary hemodynamics or who refuse prostaglandin therapy. If phosphodiesterase-5 inhibitor monotherapy is used, close follow-up for deterioration is indicated.

12.8.3 Calcium Channel Blockers

Patients with PAH who have an acute response to inhaled vasodilators such as nitric oxide (a drop in mPAP of 10–40 mmHg with preserved CO) are candidates for treatment with a calcium channel blocker and have a substantially improved prognosis, compared to patients without an acute vasodilator response [38]. A durable response to calcium channel blocker therapy during pregnancy has been described [10]. In the only prospective registry of pregnant patients with PAH, 8 of 16 patients who successfully delivered a baby and survived without transplantation were acute

vasodilator responders [10]. Calcium channel blockers are considered safe in pregnancy [39]. For those patients meeting strict criteria for an acute response to inhaled nitric oxide, therapy with calcium channel antagonists is recommended [31, 38] with close follow-up, as discussed above. In pregnant PAH patients not meeting these strict criteria, there is no role for calcium channel antagonists. In this setting, calcium channel blockers may be detrimental because of their nonselective vasodilatory effects, with a concomitant drop in SVR, which, in the presence of inadequate CO, may lead to circulatory collapse.

12.8.4 Endothelin Receptor Antagonists

Endothelin receptor antagonists (ambrisentan, bosentan, macitentan, and sitaxentan) are pregnancy category X drugs and should be discontinued in a patient with PAH who is known to be pregnant because of their teratogenicity.

12.9 Special Considerations at Delivery

The approach to use of PAH therapy around the time of delivery is influenced by the drugs that the patient has taken during pregnancy, stability before planned delivery, and progress in the peripartum period. When titrating these therapies, there is a need to appreciate the physiological changes that normally occur in pregnant women and to be receptive to possible worsening of pulmonary vascular disease and the effects of drugs used in the peripartum period. Oxytocic drugs, for example, can induce hypotension and tachycardia and should always be given by slow infusion. The key to titration of these therapies is careful monitoring of patients during the peripartum period in a high-acuity environment. Insertion of a central venous catheter to allow measurement of central venous pressure and sampling of blood to assess central venous saturation and insertion of an arterial line for measurement of blood pressure and blood gas sampling are highly recommended [40]. Swan-Ganz catheterization is not routinely used because of the risk of complications but can be considered in selected cases. Noninvasive measures of CO, such as lithium dilution, can be used to titrate treatment in patients with PAH [11, 40, 41]. For patients not receiving parenteral prostanoids, a low-dose infusion of IV prostanoid started several hours before a planned Cesarean section allows the physician to assess the hemodynamic effects of this infusion and avoid problems associated with initiating prostanoids in the immediate peripartum period, when, in an unstable patient, it may be difficult to discern side effects of the drug from pulmonary hemodynamic instability. In these cases, a Swan-Ganz catheter may help with assessment of the therapeutic effects of infused prostacyclins.

If patients are receiving oral sildenafil, consideration should be given to using the IV preparation of the drug, particularly if there are concerns regarding absorption, which can occur postoperatively, for example, following development of ileus after

Cesarean section. The treatment goals during delivery are to maintain systemic and right atrial pressures, to monitor fluid balance, and to avoid volume overload, particularly in the first 48 h. A rising right atrial pressure after delivery may simply reflect fluid overload and can be managed by judicious use of diuretic therapy. If the condition deteriorates with falling central venous saturation, rising right atrial pressure, and other features suggesting worsening of pulmonary vascular status, then increasing the dose beyond the background dose of IV prostanoid is usually appropriate, sometimes coupled with inotropic therapy, such as low-dose dobutamine. For patients developing hypotension, a cause should be sought, such as bleeding, sepsis, or low-output heart failure due to increasing afterload. In this setting, once volume status has been optimized, drugs such as vasopressin or noradrenaline should be considered [42]. While the treatment recommendations above assume access to PAH therapy, supportive care should be instituted in locations where the full complement of PAH-directed therapy is not available. Such care is discussed in "pregnancy management" above.

12.10 Anticoagulation Therapy

Anticoagulation therapy is recommended for patients with PAH during pregnancy because pregnancy itself is a hypercoagulable state [13, 31, 32]. The basic rule is to prevent thrombosis in the pulmonary artery and deep vein thrombosis [33]. Even with low-dose heparin, there may be side effects of subchorionic hematoma and maternal cerebral bleeding [13]. Low-molecular-weight heparin is sometimes used in patients who have experienced subchorionic hematoma, and prophylactic heparin is recommended for all PAH patients in the peripartum period [31]. In use of low-molecular-weight heparin during pregnancy, preparation for delivery is required to facilitate rapid discontinuation if indicated. Warfarin is a teratogen and is contraindicated in pregnancy. New oral anticoagulants (e.g., dabigitran, rivaroxaban, and apixaban) are pregnancy category C drugs, and their use in PAH has not been studied; thus, they are not recommended.

References

1. Hoeper MM (2013) Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol 62:D42–D50
2. Anna RH, David GK, Barbara AC, Cockrill ZS, Victoria JW, Manak AH et al (2015) Statement on pregnancy in pulmonary hypertension from the pulmonary vascular research institute. Pulm Circ 5(3):435–465
3. Bonnin M, Mercier FJ, Sitbon O, Roger-Christoph S, Jaïs X, Humbert M, Audibert F, Frydman R, Simonneau G, Benhamou D (2005) Severe pulmonary hypertension during pregnancy: mode of delivery and anesthetic management of 15 consecutive cases. Anesthesiology 102(6):1133–1137. discussion 5A–6A
4. Katsuragi S, Yamanaka K, Neki R, Kamiya C, Sasaki Y, Osato K, Miyoshi T et al (2012) Maternal outcome in pregnancy complicated with pulmonary arterial hypertension. Circ J 76(9):2249–2254

5. Bédard E, Dimopoulos K, Gatzoulis MA (2009) Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? Eur Heart J 30(3):256–265
6. Monnery L, Nanson J, Charlton G (2001) Primary pulmonary hypertension in pregnancy; a role for novel vasodilators. Br J Anaesth 87(2):295–298
7. Duarte AG, Thomas S, Safdar Z, Torres F, Pacheco LD, Feldman J, deBoisblanc B (2013) Management of pulmonary arterial hypertension during pregnancy: a retrospective., multicenter experience. Chest 143(5):1330–1336
8. Ma L, Liu W, Huang Y (2012) Perioperative management for parturients with pulmonary hypertension: experience with 30 consecutive cases. Front Med 6(3):307–310
9. Rosengarten D, Blieden LC, Kramer MR (2012) Pregnancy outcomes in pulmonary arterial hypertension in the modern management era. Eur Respir J 40(5):1304–1305
10. Jaïs X, Olsson KM, Barberà JA, Blanco B, Torbicki A, Peacock A, Vizza CD, Macdonald P, Humbert M, Hoeper MM (2012) Pregnancy outcomes in pulmonary arterial hypertension in the modern management era. Eur Respir J 40(4):881–885
11. Kiely DG, Condliffe R, Webster V, Mills GH, Wrench I, Gandhi SV, Selby K et al (2010) Improved survival in pregnancy and pulmonary hypertension using a multiprofessional approach. BJOG 117(5):565–574
12. Curry RA, Fletcher C, Gelson E, Gatzoulis MA, Woolnough M, Richards N, Swan L, Steer PJ, Johnson MR (2012) Pulmonary hypertension and pregnancy—a review of 12 pregnancies in nine women. BJOG 119(6):752–761
13. Regitz-Zagrosek V, Lundqvist CB, Borghi C, Cifkova R, Ferreira R, Foidart JM, Gibbs JSR et al (2011) ESC guidelines on the management of cardiovascular diseases during pregnancy: the task force on the Management of Cardiovascular Diseases during pregnancy of the European Society of Cardiology (ESC). Eur Heart J 32(24):3147–3197
14. Pieper PG, Hoendermis ES (2011) Pregnancy in women with pulmonary hypertension. Neth Heart J 19(12):504–508
15. Wexler ID, Johannesson M, Edenborough FP, Sufian BS, Kerem E (2007) Pregnancy and chronic progressive pulmonary disease. Am J Respir Crit Care Med 175(4):300–305
16. Jain JK, Mishell DR Jr (1994) A comparison of intravaginal misoprostol with prostaglandin E2 for termination of second-trimester pregnancy. N Engl J Med 331(5):290–293
17. Pitkin RM, Perloff JK, Koos BJ, Beall MH (1990) Pregnancy and congenital heart disease. Ann Intern Med 112:445–454
18. Svetlichnaya J, Janmohammed M, De Marco T (2016) Special situations in pulmonary hypertension: pregnancy and right ventricular failure. Cardiol Clin 34:473–487
19. Liu S, Liston RM, Joseph KS, Heaman M, Sauve R, Kramer MS (2007) Maternal mortality and severe morbidity associated with low-risk planned cesarean delivery versus planned vaginal delivery at term. Can Med Assoc J 176(4):455–460
20. Heerdt PM, Caldwell RW (1989) The mechanism of nitrous oxide-induced changes in pulmonary vascular resistance in a dog model of left atrial outflow obstruction. J Cardiothorac Anesth 3(5):568–573
21. Sørensen MB, Jacobsen E (1977) Pulmonary hemodynamics during induction of anesthesia. Anesthesiology 46(4):246–251
22. Hoeper MM, Granton J (2011) Intensive care unit management of patients with severe pulmonary hypertension and right heart failure. Am J Respir Crit Care Med 184(10):1114–1124
23. Duggan AB, Katz SG (2003) Combined spinal and epidural anaesthesia for caesarean section in a parturient with severe primary pulmonary hypertension. Anaesth Intensive Care 31(5):565–569
24. Le RJ, Fenstad ER, Maradit-Kremers H, McCully RB, Frantz RP, MD MG, Kane GC (2011) Syncope in adults with pulmonary arterial hypertension [retracted in J am Coll Cardiol 59(21):1919]. J Am Coll Cardiol 58(8):863–867
25. Brignole M, Alboni P, Benditt DG, Bergfeldt L, Blanc JJ, Bloch Thomsen PE, van Dijk JG et al (2004) Guidelines on management (diagnosis and treatment) of syncope—update 2004: executive summary. Eur Heart J 25(22):2054–2072

26. Yarlagadda S, Poma PA, Green LS, Katz V (2010) Syncope during pregnancy. Obstet Gynecol 115(2):377–380
27. Elliot CA, Stewart P, Webster VJ, Mills GH, Hutchinson SP, Howarth ES, Bu'Lock FA, Lawson RA, Armstrong IJ, Kiely DG (2005) The use of iloprost in early pregnancy in patients with pulmonary arterial hypertension. Eur Respir J 26(1):168–173
28. Bédard E, McCarthy KP, Dimopoulos K, Giannakoulas G, Gatzoulis MA, Ho SY (2009) Structural abnormalities of the pulmonary trunk in tetralogy of Fallot and potential clinical implications: a morphological study. J Am Coll Cardiol 54(20):1883–1890
29. Brittain EL, Pugh ME, Wheeler LA, Robbins IM, Loyd JE, Newman JH, Austin ED, Hemnes AR (2013) Prostanoids but not oral therapies improve right ventricular function in pulmonary arterial hypertension. JACC Heart Failure 1(4):300–307
30. Waxman AB, Zamanian RT (2013) Pulmonary arterial hypertension: new insights into the optimal role of current and emerging prostacyclin therapies. Am J Cardiol 111(5):1A–16A. quiz 17A–19A
31. Barst RJ, Gibbs JS, Ghofrani HA, Hoeper MM, McLaughlin VV, Rubin LJ, Sitbon O, Tapson VF, Galiè N (2009) Updated evidence-based treatment algorithm in pulmonary arterial hypertension. J Am Coll Cardiol 54(1 suppl):S78–S84
32. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA et al (2009) ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation task force on expert consensus documents and the American Heart Association: developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J Am Coll Cardiol 53(17):1573–1619
33. Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiéry JL, Barberà JA, Beghetti M et al (2009) Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 34(6):1219–1263
34. Hsu CH, Gomberg-Maitland M, Glassner C, Chen JH (2011) The management of pregnancy and pregnancy-related medical conditions in pulmonary arterial hypertension patients. Int J Clin Pract Suppl 65:6–14
35. Decoene C, Bourzoufi K, Moreau D, Narducci F, Crepin F, Krivosic-Horber R (2001) Use of inhaled nitric oxide for emergency cesarean section in a woman with unexpected primary pulmonary hypertension. Can J Anaesth 48(6):584–587
36. Goland S, Tsai F, Habib M, Janmohamed M, Goodwin TM, Elkayam U (2010) Favorable outcome of pregnancy with an elective use of epoprostenol and sildenafil in women with severe pulmonary hypertension. Cardiology 115(3):205–208
37. LeVarge BL (2015) Prostanoid therapies in the management of pulmonary arterial hypertension. Ther Clin Risk Manag 11:535–547
38. Sitbon O, Humbert M, Jaïs X, Ioos V, Hamid AM, Provencher S, Garcia G, Parent F, Hervé P, Simonneau G (2005) Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation 111(23):3105–3111
39. Simhan HN, Caritis SN (2007) Prevention of preterm delivery. N Engl J Med 357(5):477–487
40. Kiely DG, Elliot CA, Wilson VJ, Stewart P (2006) Pregnancy and pulmonary hypertension: new approaches to the management of a life threatening condition. In: Steer PH, Gatzoulis MA, Baker P (eds) Heart disease and pregnancy. RCOG Press, London, pp 211–229
41. Jonas MM, Tanser SJ (2002) Lithium dilution measurement of cardiac output and arterial pulse waveform analysis: an indicator dilution calibrated beat-by-beat system for continuous estimation of cardiac output. Curr Opin Crit Care 8(3):257–261
42. Kiely DG, Condliffe R, Wilson VJ, Gandhi SV, Elliot CA (2013) Pregnancy and pulmonary hypertension: a practical approach to management. Obstet Med 6(4):144–154

Aortic Disorder

13

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Abstract

Exposure of estrogen and hemodynamic changes during pregnancy lead to fragility of the elastic fiber of the aortic media. This elevates the risk for aortic dilatation and dissection. Cystic medial necrosis changes in the aortic wall media occur during pregnancy, and the diameter of the aorta increases slightly. These phenomena are generally referred to as aortopathy and are particularly important in management of patients with connective tissue diseases such as Marfan syndrome during pregnancy and in postpartum. A large sinus of Valsalva, increased aortic size index, and rapid growth of the sinus of Valsalva are risk factors for aortic dilatation or dissection in pregnant Japanese women with Marfan syndrome.

Keywords

Aortic dissection · Marfan syndrome · Pregnancy · Sinus of Valsalva · Aortic size index

13.1 Hemodynamic Changes in Pregnancy and Aortopathy

In normal pregnancy, total blood volume increases by 40–50%, heart rate increases about 20% above baseline, and cardiac output may be 30–50% above baseline by the end of the second trimester. Peripheral resistance decreases by 16 weeks of

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gestation to allow increased uterine blood flow but becomes higher than before conception due to increased levels of renin and angiotensin II. These hemodynamic changes may cause dilatation and dissection of the aorta, particularly for a patient with a weak aortic media, such as that in Marfan syndrome and Loeys-Dietz syndrome.

13.1.1 High Level of Estrogen and Aortopathy

The estrogen level is high in normal pregnancy to support growth of the uterus, fetus, and mammary gland. Exposure to estrogen during pregnancy leads to fragility of the elastic fiber of the aortic media (elastic fiber fragmentation). This elevates the risk for aortic dilatation and dissection, affects the renin-angiotensin system, elevates extracellular fluid and volume load, and increases vulnerability of the aortic wall. Cystic medial necrosis changes in the aortic wall media during pregnancy, and the diameter of the aorta increases slightly.

13.2 Marfan Syndrome and Pregnancy

Marfan syndrome is an autosomal dominant connective tissue disorder caused by mutations in the fibrillin-1 (FBN1) gene located on chromosome 15 [1]. These mutations result in weakness of supportive tissue and clinical characteristics of cardiovascular, skeletal, and ocular systems [2, 3]. Cardiovascular complications are the main cause of morbidity and mortality in patients with Marfan syndrome [4]. Before preventive surgical approaches to aortic disease, the mean life expectancy for a patient with Marfan syndrome was below 40 years old, with aortic dissection, aortic rupture, and cardiac failure being the main causes of death [5]. However, beta-blocker therapy and elective surgical repair have increased life expectancy to close to normal [6].

Pregnancy is strongly associated with life-threatening problems in Marfan patients. The risk of aortic dilatation or dissection increases during and after pregnancy in these patients due to superimposition of the hyperdynamic and hypervolemic circulatory state of pregnancy on the preexisting weakness of the aortic media [3]. The rate of aortic dissection in pregnancy has been examined widely. In 1981, Pyeritz found no aortic complications in 105 pregnancies in 26 women affected by Marfan syndrome, based on phone interviews [7]. Rossiter et al. prospectively followed 45 pregnancies in 21 women and found 2 cases complicated by dissection [8]; Lipscomb et al. reported 6 aortic events, including 4 aortic dissections, in 91 pregnancies in 36 women [9]; Lind et al. found 5 aortic dissections in 117 pregnancies [10]; and Pacini et al. reported 7 aortic dissections in 160 pregnancies in 85 women [11]. Combining all these data gives a risk of 3.9% for aortic complication during pregnancy in women with Marfan syndrome who are not taking beta-blockers.

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

The risk factors for aortic complications in pregnant patients affected with Marfan syndrome have not been examined with inclusion of a consideration of the body surface area. Therefore, to permit appropriate consultation and management of patients, we studied 29 consecutive pregnant patients with Marfan syndrome in one institution to determine the factors that influence maternal aortic complications.

13.2.1 Pregnancy in Japanese Patients with Marfan Syndrome

We retrospectively analyzed 29 consecutive pregnant patients with Marfan syndrome who were managed at the National Cerebral and Cardiovascular Center from 1991 to 2013. Diagnosis of Marfan syndrome was made based on the original Ghent criteria (1996) [18]. The cases were divided into patients with aortic dilatation or dissection (group D, $n = 12$) during pregnancy or within 1 year after delivery and those without aortic dilatation or dissection (group ND, $n = 17$). Aortic dilatation was defined as a diameter of >60 mm at any part of the aorta.

13.2.1.1 Measurement of the Aortic Diameter and Indication for Surgery

Measurement of the sinus of Valsalva was made by echocardiography in two-dimensional parasternal long-axis views at end-diastole using the leading edge to leading edge method [16, 19]. MRI and CT were not routinely used. The Japanese Circulation Society recommends an operation for patients with a sinus of Valsalva over 5 cm (class IIa, level C) in all Marfan syndrome cases [20]. Some surgeons also recommend an operation for patients with a sinus of Valsalva over 4.5 cm [21]. In our institution, surgical intervention is indicated according to the above criteria and for patients with a family history of dissection or sudden death. In general, surgical intervention is indicated for a sinus of Valsalva over 4.0 cm or in a case with steady aortic size growth [22, 23]. During pregnancy, surgical intervention is indicated if there is steady aortic growth or massive dissection. To standardize the measurement

based on body size, we expressed the size of the sinus of Valsalva using the aortic size index (ASI), which is calculated as ASI = aortic diameter (mm)/body surface area (m^2) [17].

13.2.1.2 Management During Pregnancy

Echocardiographic follow-up including aortic diameter measurement and a Holter electrocardiogram are necessary at least once in each trimester during pregnancy and within 4 weeks after delivery. If the aortic root diameter is ≥40 mm, echocardiography is needed every 2 weeks in the second and third trimester. Marfan syndrome is also occasionally complicated with mitral valve regurgitation. In some of these cases, the level of regurgitation progresses from mild to severe during pregnancy, and the number of arrhythmias increases. In these cases, a Holter electrocardiogram is useful to determine if an increase in dose or introduction of beta-blockade is required. When surgical intervention is indicated, the operation should be performed after Cesarean section for a mature fetus. If the fetus is too immature to live independently, the operation should be performed with the fetus in utero.

13.2.2 Aortic Risks During Pregnancy in Japanese Patients with Marfan Syndrome

13.2.2.1 Cases with Aortic Dilatation or Dissection

Twelve cases had aortic dilatation or dissection associated with pregnancy, including seven that occurred during pregnancy and five within 1 year after pregnancy. Two of the 7 antepartum cases showed aortic dilatation >60 mm (maximum diameter of the aorta) in the second trimester at 16 and 19 weeks of gestation, respectively. One case underwent hemiarch replacement, and the other underwent a David operation under cardiopulmonary bypass with the fetus in utero. The other 5 dissections during pregnancy occurred at 29, 33, 34, 35, and 39 weeks of gestation. After delivery by Cesarean section, three of these patients underwent Bentall operations, and two received conservative therapy. Dissection in the 5 postpartum cases occurred at 4 days and 1, 8, 11, and 18 months after delivery. Of the 12 dilatation or dissection cases, 9 occurred in the ascending aorta, 1 in the descending aorta, and 2 in both locations.

13.2.2.2 Demographic Data in Cases with and Without Aortic Dilatation or Dissection

Maternal age, week of delivery, and birth weight did not differ between groups D (aortic dilatation or dissection) and ND (no dilatation or dissection) (Table 13.1). The incidence of Cesarean section tended to be higher in group D than in group ND (8/12, 66.7% vs. 3/17, 17.6%, $P < 0.1$), due to performance of Cesarean section in cases in which dilatation or dissection of the aorta occurred during pregnancy. The number of patients meeting each diagnostic category for Marfan syndrome (Ghent criteria 1996) [18] is shown in Table 13.2. In group D, fewer patients met the major

Table 13.1 Clinical features of patients with and without aortic dilatation or dissection

	Group D (n = 12)	Group ND (n = 17)	P value
Maternal age	29.8 ± 3.3	30.1 ± 4.0	ns
Height (cm)	167.2 ± 4.4	165.3 ± 4.2	ns
Weight (kg)	65.9 ± 4.6	64.5 ± 3.9	ns
Nulli-/multiparous	8/4	12/5	ns
Weeks of delivery	36.0 ± 3.3	37.0 ± 2.8	ns
Birth weight (g)	2722 ± 711	2769 ± 599	ns
Delivery mode			ns (p = 0.07)
Vaginal delivery	4	14	
Cesarean section	8	3	
BMI	23.2 ± 1.4	23.1 ± 1.8	ns
DM	2	3	ns
Hypertension	2	3	ns
Smoking	2	3	ns

Group D aortic dilatation or dissection, *Group ND* no aortic dilatation or dissection, *BMI* body mass index, *DM* diabetes mellitus, *ns* not significant
Maternal age, height, weight, weeks of delivery, birth weight, and BMI are shown as means ± SD and were analyzed by student t-test. Other data were analyzed by chi-square test and Fisher exact test. $P < 0.05$ indicates a significant difference

Table 13.2 Number of patients meeting each diagnostic category for Marfan syndrome

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

Group D aortic dilatation or dissection, *Group ND* no aortic dilatation or dissection
The number of patients meeting each diagnostic category for Marfan syndrome (Ghent criteria [18]) is shown. Data were analyzed by chi-square test and Fisher exact test
* $P < 0.05$

ocular criteria (2/10, 20% vs. 8/12, 67%, $P < 0.05$), and more patients met the major cardiovascular criteria (10/10, 100% vs. 7/12, 58%, $P < 0.05$). Gene analysis was performed in 11 of the 29 cases (38%), and a fibrillin-1 mutation was found more commonly in group D, although the difference was not significant (4/4, 100% vs. 4/7, 57%, $P = 0.06$). A family history of sudden death or aortic dissection was more frequent in group D (7/12, 58% vs. 4/17, 24%, $P < 0.05$).

13.2.2.3 Echocardiographic Data in Cases with and Without Aortic Dilatation or Dissection

The sinus of Valsalva in the first trimester of pregnancy was significantly larger in group D than in group ND (mean (range) values, 44.1 (36–61) vs. 34.8 (28–45) mm,

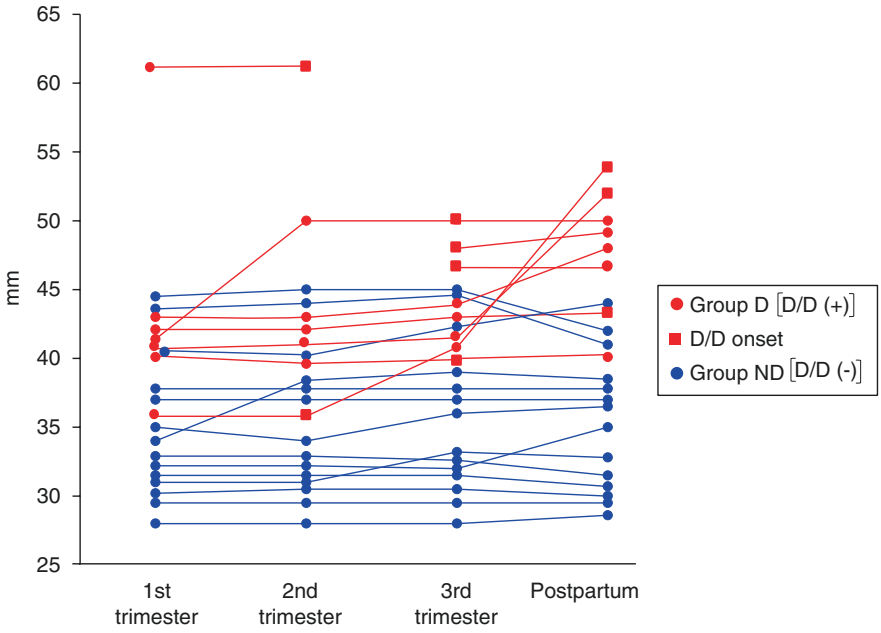

Fig. 13.1 Diameters of the sinus of Valsalva. D/D indicates aortic dilatation or dissection. Cases with and without aortic dilatation or dissection are shown by red and blue circles, respectively (groups D and ND, respectively). Pink squares indicate a cardiac event. In the first trimester, a larger sinus of Valsalva was found in group D compared to group ND (41.5 ± 2.4 vs. 34.8 ± 1.3, $P < 0.05$ by student t-test). The sinus of Valsalva was ≥40 mm in 6/7 cases in group D and in 3/14 cases in group ND ($P < 0.05$ by chi-square test and Fisher exact test)

$P < 0.005$; Fig. 13.1, Table 13.3), and a sinus of Valsalva ≥40 mm in the first trimester was more frequent in group D (6/7, 86% vs. 3/14, 21%, $P < 0.05$) (Fig. 13.1).

An aortic size index (ASI) (diameter of the sinus of Valsalva/body surface area) ≥25 mm/m^2 was more frequent in group D than in group ND (7/7, 100% vs. 0/14, 0%, $P < 0.0001$) (Fig. 13.2). In ROC analysis of the relationship of the ASI in the first trimester with aortic dilatation or dissection during pregnancy and postpartum, the area under the curve (AUC) was 0.985, and the size of the sinus of Valsalva that showed the best sensitivity (1-specificity) was 25 mm/m^2. In one case, aortic dissection occurred in a patient with a sinus of Valsalva of only 36 mm in the first trimester. However, her ASI was 27.3 mm/m^2 (36 mm/1.31 m^2), which was the fifth largest in the study. This indicates that adjustment of the size of the sinus of Valsalva using body surface area is more appropriate for prediction of aortic dilatation or dissection, compared to the absolute diameter. Significantly faster growth of the sinus of Valsalva was also observed in group D (median [interquartile range] values, 0.41 [0.23–0.66] vs. 0.05 [−0.13–0.22] mm/month, $P < 0.05$; Fig. 13.3).

The sizes of the right and left ventricles did not differ between the two groups (Table 13.3). In the first trimester, patients in group D showed more frequent moderate to severe aortic valve regurgitation (6/12, 50% vs. 2/17, 12%, $P < 0.05$) and

Table 13.3 Echocardiographic findings in patients with and without aortic dilatation or dissection

Item	Group D (n = 12)	Group ND (n = 17)	P value
Sinus of Valsalva (mm) in first trimester	44.0 ± 10.0	34.8 ± 5.5	<0.005
Growth of aorta (mm/month)	0.41 [0.23–0.66]	0.05 [−0.13–0.22]	<0.005
Aortic valve regurgitation			
None-mild	6	15	<0.05
Moderate-severe	6	2	
Mitral valve prolapse	6	3	<0.05
LVDd	45.8 ± 7.1	44.8 ± 6.8	ns
LVDs	31.1 ± 4.7	30.1 ± 4.6	ns
%FS	36.5 ± 5.6	37.5 ± 4.6	ns
RA cavity enlarged	2	3	ns
RV cavity enlarged	2	2	ns
PA dilatation (≥20 mm)	3	2	ns

LVDd left ventricle end-diastolic dimension, *LVDs* left ventricle end-systolic dimension, *%FS* fractional shortening, *RA* right atrium, *RV* right ventricle, *PA* pulmonary artery, *ns* not significant
$P < 0.05$ indicates a significant difference. Sinus of Valsalva, LVDd, LVDs, %FS, were analyzed by student t-test and are shown as the mean ± SD. Growth of the aorta is shown as the median [interquartile range], and the data were analyzed by Wilcoxon test. Other data were analyzed by chi-square test and a Fisher exact test

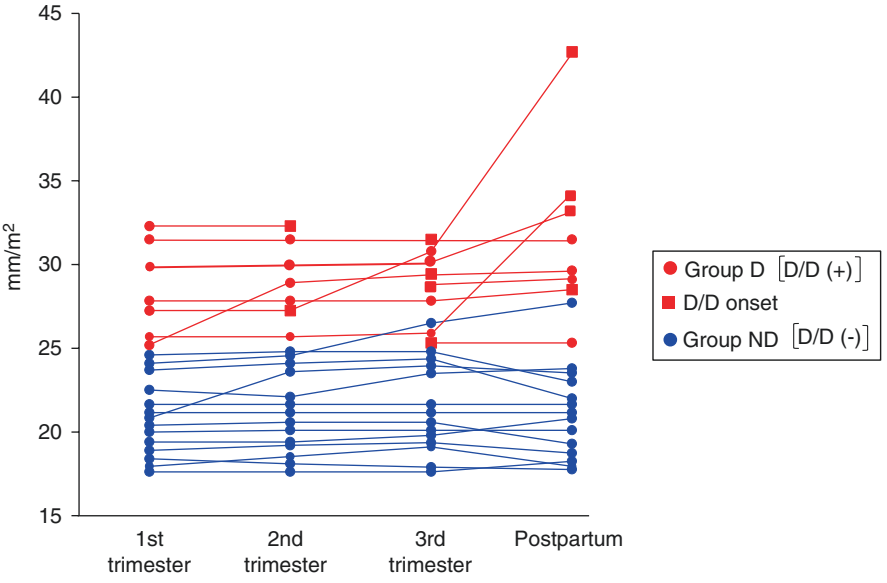

Fig. 13.2 Adjusted sizes of the sinus of Valsalva (size of the sinus of Valsalva/body surface area: mm/m^2). D/D indicates aortic dilatation or dissection. Cases with and without aortic dilatation or dissection are shown by red and blue circles, respectively (groups D and ND, respectively). In the first trimester, the adjusted size of the sinus of Valsalva was ≥25 mm/m^2 in 7/7 cases in group D and in 0/14 cases in group ND ($P < 0.0001$ by chi-square test and Fisher exact test)

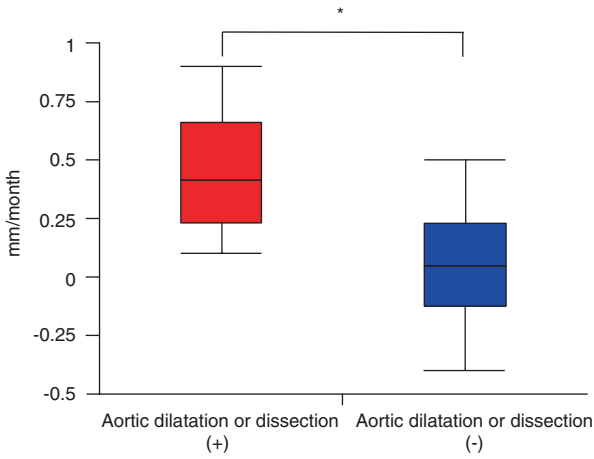

Fig. 13.3 Rate of growth of the sinus of Valsalva. Significantly faster growth of the sinus of Valsalva was observed in group D (red box) compared to group ND (blue box). The middle bar indicates the 50th percentile; box edges are the 25th and 75th percentiles; and outer bars are the 10th and 90th percentiles. Data were analyzed by Wilcoxon test. *$P < 0.05$

mitral valve regurgitation (7/12, 58% vs. 3/17, 18%, $P < 0.05$). These effects were already present before conception and may be one of the causes of dilatation or dissection.

13.2.3 Risk Factors for Aortic Dilatation or Dissection

Risk factors for pregnancy-associated dilatation or dissection in Japanese patients with Marfan syndrome differed significantly between groups D and ND and were mostly consistent with those found in previous studies [7–10, 14]. These factors include a large sinus of Valsalva, rapid growth of the sinus of Valsalva during pregnancy, moderate to severe aortic valve or mitral valve regurgitation, and a family history of sudden death or aortic dissection. We found that a large sinus of Valsalva (≥40 mm) at the start of pregnancy was a risk factor for dilatation or dissection during pregnancy and postpartum. Our results differ from findings in a relatively large prospective study [15], in which it was concluded that pregnancy in women with Marfan syndrome is relatively safe up to an aortic root diameter of 45 mm and with Canadian guidelines [23] that recommend that women with an aortic root diameter beyond 44 mm should be strongly discouraged from becoming pregnant. Taking into account that Japanese women have generally smaller physiques than Europeans and North Americans, we recommend that the cutoff for Japanese patients for advice regarding avoidance of pregnancy should be a sinus of Valsalva diameter ≥40 mm, rather than ≥45 mm. In a case report of a patient who developed massive retrograde type B aortic dissection 7 days after normal spontaneous vaginal delivery, Silversides et al. [24] described the patient as “petite” (body surface area, 1.69 m^2); however, this measurement is larger than that in the average Japanese woman.

13.2.4 Use of the Adjusted Aortic Size Index for Women with Small Physiques

We also suggest that the diameter of the sinus of Valsalva adjusted for body surface area (diameter of the Valsalva/body surface area, mm/m^2) may be more appropriate for detection of high-risk cases at the start of pregnancy. The relative aortic size was first used to predict complications in patients with thoracic aortic aneurysms [17]. We found that an aortic size index (ASI) ≥25 mm/m^2 in the first trimester has a high risk for aortic dilatation or dissection during pregnancy and postpartum. The ASI is a novel measurement of relative aortic size that predicts rupture of aortic aneurysm [17], and Davies et al. found that the ASI was more important than absolute aortic size in predicting aortic complications, especially in smaller women such as those in the Japanese population [17]. We found more rapid growth of the sinus of Valsalva in patients with Marfan syndrome with pregnancy-associated aortic dilatation or dissection, compared to those without these conditions. Therefore, even if the diameter of the sinus of the Valsalva is small, rapid growth carries a risk of aortic dissection or dilatation. The same phenomenon has been reported in nonpregnant cases of Marfan syndrome.

Gandhi et al. [25] followed 108 women with Marfan syndrome and aortic root growth prospectively using serial echocardiograms and found that the patients could be divided into two normally distributed groups based on aortic growth rates: 90% were slow growers and 10% were fast growers. Significantly more dissections of the ascending aorta (25% vs. 4%, $P < 0.001$) were observed in the fast growers, and the average growth of the sinus of Valsalva in the fast group was 1.8 mm/year. The median growth in the five dissected cases in our study was as high as 4.1 mm/year. This large increase relative to that in Gandhi et al. [25] is probably due to the maternal cardiovascular changes in pregnancy, including increased blood volume, heart rate, and stroke volume [15]. Furthermore, hormonally mediated histological changes also occur in the aorta, including a decrease in mucopolysaccharides and loss of elastic fibers in the aortic wall [26–28]. Therefore, care is required in treating patients with a high growth rate of the sinus of Valsalva. The frequency and degree of aortic and mitral valve regurgitation were also higher in cases with aortic dilatation or dissection, and these valvular changes may have been the causes of dilatation or dissection.

An international expert panel established the revised Ghent criteria in 2010, in which more weight was placed on cardiovascular manifestations, and the cardinal clinical features are aortic dilatation/dissection and ectopia lentis [29]. In these revised criteria, a more prominent role was also given to molecular genetic testing of FBN1 and other relevant genes in diagnostic assessment, while some less specific manifestations of Marfan syndrome were removed or made less influential in the diagnostic evaluation. The new criteria also try to differentiate Marfan syndrome from Marfan-related syndromes such as Loeys-Dietz syndrome, Ehlers-Danlos syndrome, and familial thoracic aortic aneurysm, which are associated with a significantly greater risk of cardiovascular problems [29–31]. In our study, fewer patients

with dilatation or dissection of the aorta met major ocular criteria, but more met major cardiovascular criteria and had a more frequent family history of dilatation or dissection. These findings indicate that the new diagnostic criteria for Marfan syndrome facilitate more accurate identification of high-risk patients for pregnancy-associated dilatation or dissection.

13.3 Marfan-Related Disorder/Other Aortopathies and Pregnancy

13.3.1 Loeys-Dietz Syndrome and Pregnancy

Loeys-Dietz syndrome (LDS) is an autosomal dominant connective tissue disorder characterized by aortic aneurysms and generalized arterial tortuosity, hypertelorism, and bifid/broad uvula or cleft palate that was first described in 2005 [32, 33]. Arterial tortuosity can be general but commonly involves the head and neck vessels (Fig. 13.4a). Arterial aneurysms have been observed in almost all side branches of the aorta, including the subclavian, coronary, supermesenteric, hepatic, renal, and iliac artery (Fig. 13.4b). Rapidly progressive aortic aneurysmal disease is a distinct feature of LDS that requires close monitoring. Patients with LDS 1/2 with severe craniofacial features are at particularly high risk and have ruptures at early ages and at smaller dimensions than those with other aneurysm syndromes [32, 33]. Aortic dissection occurs in patients as young as 3 months, and cerebral hemorrhage can occur at 3 years [34, 35]. Initial reports of LDS 1/2 cohorts described a mean age of

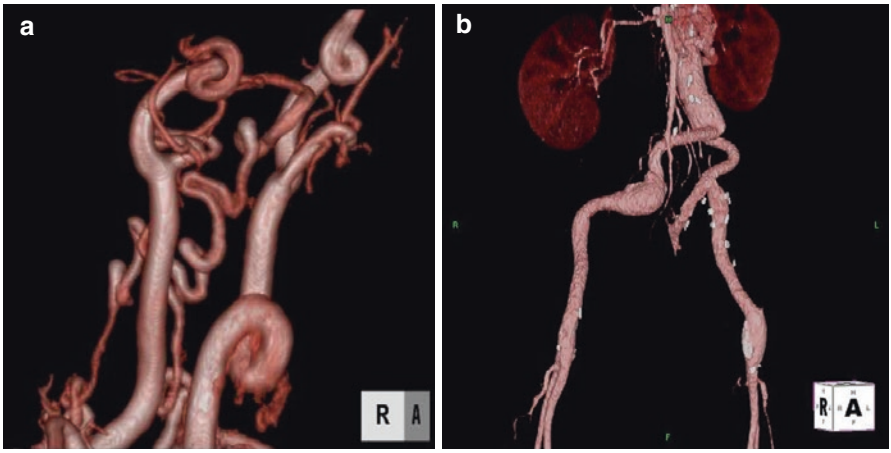

Fig. 13.4 (**a**) Arterial tortuosity at neck vessels in Loeys-Dietz syndrome. Arterial tortuosity can be general but commonly involves the head and neck vessels. (**b**) Arterial aneurysm in Loeys-Dietz syndrome at the iliac artery. Arterial aneurysms have been observed in almost all side branches of the aorta, including the subclavian, coronary, supermesenteric, hepatic, renal, and iliac artery in Loeys-Dietz syndrome

death at 26.1 years, with aortic dissection and cerebral hemorrhage as major causes of death [32]. Better detection, surveillance, and early treatment are expected to extend the life span of affected individuals.

Women with LDS can have successful pregnancies and deliveries, although pregnancies should be considered high risk. In the absence of predictive factors for complications, counseling women on specific risks remains a challenge. In 21 pregnancies in 12 women with LDS 1/2, 6 women had a major complication during pregnancy or immediately postpartum, comprising 4 aortic dissections and 2 uterine ruptures [32]. These occurred in first, second, and third pregnancies. Two other women experienced severe uterine hemorrhage independent of pregnancy. Arterial rupture may also be a pregnancy or postpartum complication. Cardiovascular drugs can be used with safe down-titration and discontinuation of angiotensin receptor blockers prior to becoming pregnant. Beta-blocker usage is recommended throughout pregnancy. Use of pain, anticoagulation, and other drugs should be discussed prior to pregnancy to reduce teratogenic effects on the fetus. Early delivery and avoidance of high intra-abdominal pressure by Cesarean section may reduce the risk of obstetric complications. However, no specific recommendations can be made due to the absence of studies comparing the efficacy of Cesarean and vaginal deliveries.

13.3.2 Ehlers-Danlos Syndrome and Pregnancy

Ehlers-Danlos syndrome (EDS) is a multifaceted condition that has several different types that affect patients in different ways. The most serious is type 4 or vascular EDS. A female patient diagnosed with this type should understand that pregnancy is very risky and potentially life-threatening due to a high risk of catastrophic arterial or organ rupture. A study published in 2014 found that pregnancy-related deaths in women with vascular EDS occurred in 30 of 565 deliveries (5.3%) [36]. Interviews with 39 women indicated that 46% had uncomplicated pregnancies, while the most common pregnancy-related complications were third- or fourth-degree lacerations (20%) and preterm delivery (19%). Life-threatening complications occurred in 14.5% of deliveries and included arterial dissection/rupture (9.2%), uterine rupture (2.6%), and surgical complications (2.6%).

13.3.3 Turner Syndrome and Pregnancy

Ovarian failure is a typical feature in Turner syndrome (TS). Therefore, hormone replacement therapy (HRT) is necessary for development of normal female sexual characteristics and to prevent cardiovascular complications and osteoporosis. Spontaneous puberty occurs in 5–10% of women with TS and only 2–5% become pregnant spontaneously [37]. Oocyte donation is a treatment option for infertility of women with TS. Excellent results have been obtained with 46% of embryo transfers resulting in pregnancy, but the pregnancies carry high risks and should be followed up carefully. Children born following oocyte donation have no additional risks.

Risks can be reduced by transferring only one embryo at a time to the uterus, thus avoiding twin pregnancies. Ovarian tissue from young girls with TS can be cryopreserved for future infertility treatment, but the optimal age of ovarian biopsy is unclear, and methods of replantation and maturation of oocytes in vitro have still to be developed. Fertility counseling has become important in treatment of girls with TS. Thoracic vascular anomalies are common in TS. In 85 adult women with TS who were not preselected for cardiovascular disease, a high prevalence of aortic anomalies was seen, including elongation of the transverse arch (49%), aortic coarctation (12%), and aberrant right subclavian artery (8%) [38]. Venous anomalies were also prominent, including persistent left superior vena cava (13%) and partial anomalous pulmonary venous return (13%) [38]. The highly significant association between neck webbing, increased chest diameter, and these vascular anomalies suggests that in utero, centrally localized lymphatic obstruction may contribute to cardiovascular deformities in TS.

13.3.4 Noonan Syndrome and Pregnancy

Noonan syndrome (NS) is a genetic disorder characterized by short stature, distinctive facial features, heart defects, bleeding problems, and skeletal abnormalities [39]. Early diagnosis improves clinical management and genetic counseling. Most patients with NS have normal intelligence, but some may have special educational needs or intellectual disability. NS occurs in about 1 in 2500 births. Since NS is an autosomal dominant condition, the inheritance rate is 50%. In molecular prenatal genetic testing, DNA is isolated from cells of the developing baby by chorionic villus sampling or amniocentesis and is analyzed for the disease-causing mutation. With appropriate counseling, a parent can then decide whether to carry the pregnancy to term or to end the pregnancy. In 293 patients with NS, cardiovascular disease was seen in 81% (237), including pulmonary stenosis in 57%, atrial septal defects in 32%, and hypertrophic cardiomyopathy in 16% [40]. A genetic mutation in the Ras-MAPK signaling pathway was identified in 62% ($n = 136$). Genotype-phenotype associations were noted for PTPN11 mutations with arterial septal defects ($p = 0.001$) and pulmonary stenosis ($p < 0.001$), and RAF1 mutations were associated with hypertrophic cardiomyopathy ($p < 0.001$). Diagnosis of NS in a patient with pulmonary stenosis or infant-onset hypertrophic cardiomyopathy facilitates condition-specific counseling on outcome and prognosis.

13.4 Genetics and Preconception Counseling

Differential diagnoses of Marfan syndrome include LDS, familial thoracic aortic aneurysm, and EDS. These are autosomal dominant connective tissue disorders for which the responsible genes are known. Preconception genetic counseling is required to address the risk of recurrence and discuss diagnostic testing options. The recurrence risk is 50%. Prenatal diagnosis through amniocentesis or chorionic villus

sampling is an option for autosomal dominant connective tissue disorders. This information should be provided to the mother and father by a clinical geneticist before conception. Angiotensin-converting enzyme inhibitors should not be used during pregnancy because they are toxic against the fetal kidney, show teratogenicity of congenital heart disease, and decrease amniotic fluid volume. In a survey of pregnancy with cardiovascular disease, fetal growth restriction was found at rates of 7, 26, and 3% in alpha-/beta-adrenergic blocker, beta-adrenergic blocker, and control groups, respectively ($p < 0.05$) (to be submitted, Kayo et al.), and was dependent on the type of beta-blockade (atenolol, propranolol > metoprolol, bisoprolol).

13.5 Multidisciplinary Team Approach

A multidisciplinary team approach is important for diagnosis and management of Marfan syndrome during pregnancy, including a medical geneticist for genetic tests and preconceptional counseling. In our institution, surgical intervention is indicated according to published criteria [29] and for patients with a family history of dissection or sudden death. In general, valve-sparing aortic root replacement is indicated for a sinus of Valsalva >4.0 cm or in a case with steady aortic size growth [22, 23]. Vaginal delivery with epidural anesthesia is recommended.

13.6 Summary

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

References

1. Dietz HC, Cutting GR, Pyeritz RE, Maslen CL, Sakai LY, Corson GM et al (1991) Marfan syndrome caused by a recurrent de novo missense mutation in the fibrillin gene. Am J Hum Genet 49:662–667
2. Keane MG, Pyeritz RE (2008) Medical management of Marfan syndrome. Circulation 117:2802–2813
3. Ammash NM, Sundt TM, Connolly HM (2008) Marfan syndrome-diagnosis and management. Curr Probl Cardiol 31:7–39
4. Judge DP, Diez HC (2005) Marfan's syndrome. Lancet 366:1965–1976

5. Murdoch JL, Walker BA, Halpern BL, Kuzma JW, McKusick VA (1972) Life expectancy and causes of death in the Marfan syndrome. N Engl J Med 286:804–808
6. Silverman DI, Burton KJ, Gray J, Bosner MS, Kouchoukos NT, Roman MJ et al (1995) Life expectancy in the Marfan syndrome. Am J Cardiol 75:157–160
7. Pyeritz RE (1981) Maternal and fetal complications of pregnancy in the Marfan syndrome. Am J Med 71:784–790
8. Rossiter JP, Repke JY, Morales AJ, Murphy EA, Pyeritz RE (1995) A prospective longitudinal evaluation of pregnancy in the Marfan syndrome. Am J Obstet Gynecol 173:1599–1606
9. Lipscomb KJ, Smith JC, Bernard C, Donnai P, Harris R (1997) Outcome of pregnancy in women with Marfan's syndrome. Br J Obstet Gynaecol 104:201–206
10. Lind J, Wallenburg HC (2001) The Marfan syndrome and pregnancy: a retrospective study in a Dutch population. Eur J Obstet Gynecol Reprod Biol 98:28–35
11. Pacici L, Digne F, Boumendil A, Muti C, Detaint D, Boileau C et al (2009) Maternal complication of pregnancy in Marfan syndrome. Int J Cardiol 136:156–161
12. Goland S, Elkayam U (2009) Cardiovascular problems in pregnant women with Marfan syndrome. Circulation 119:619–623
13. Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (2003) Expert consensus document on management of cardiovascular diseases during pregnancy. Eur Heart J 24:761–781
14. Immer FF, Bansi AG, Immer-Bansi AS, McDougall J, Zehr KJ, Schaff HV et al (2003) Aortic dissection in pregnancy: analysis of risk factors and outcome. Ann Thorac Surg 76:309–314
15. Meijboom LJ, Timmermans J, Zwinderman AH, Engelfriet PM, Mulder BJ (2005) Aortic root growth in men and women with the Marfan's syndrome. Am J Cardiol 96:1441–1444
16. Roman MJ, Devereux RB, Kramer-Fox R, O'Loughlin J (1989) Two dimensional echocardiographic aortic root dimensions in normal children and adults. Am J Cardiol 64:507–512
17. Davies RR, Gallo A, Coady MA, Tellides G, Botta DM, Burke B et al (2006) Novel measurement of relative aortic size predicts rupture of thoracic aortic aneurysms. Ann Thorac Surg 81:169–177
18. De Paepe A, Devereux RB, Dietz HC, Hennekam RC, Pyeritz RE (1996) Revised diagnostic criteria for the Marfan syndrome. Am J Med Genet 62:417–426
19. Roman MJ, Rosen SE, Kramer-Fox R, Devereux RB (1993) Prognostic significance of the pattern of aortic root dilatation in the Marfan syndrome. J Am Coll Cardiol 22:1470–1476
20. JCS Joint Working Group (2006) Guidelines for diagnosis and treatment of aortic aneurysm and aortic dissection. Circ J 70:1627
21. Matsuyama K, Usui A, Akita T, Yoshikawa M, Murayama M, Yano T et al (2005) Natural history of a dilated ascending aorta after aortic valve replacement. Circ J 69:392–396
22. Davies RR, Goldstein LJ, Coady MA, Tittle SL, Rizzo JA, Kopf GS et al (2002) Yearly rupture or dissection rates for thoracic aortic aneurysms: simple prediction based on size. Ann Thorac Surg 73:17–27
23. Milewicz DM, Dietz HC, Miller DC (2005) Treatment of aortic disease in patients with Marfan syndrome. Circulation 111:e150–e157
24. Silversides CK, Kiess M, Beauchesne L, Bradley T, Connelly M, Niwa K et al (2010) Canadian Cardiovascular Society 2009 Consensus Conference on the management of adults with congenital heart disease: outflow tract obstruction, coarctation of the aorta, tetralogy of Fallot, Ebstein anomaly and Marfan's syndrome. Can J Cardiol 26:e80–e97
25. Gandhi SD, Iqbal Z, Markan S, Almassi GH, Pagel PS (2008) Massive retrograde acute type B aortic dissection in a postpartum woman with a family history of Marfan syndrome. J Clin Anesth 20:50–53
26. Whittaker PG, MacPhail S, Lind T (1996) Serial hematologic changes and pregnancy outcome. Obstet Gynecol 88:33–39
27. Hashimoto M, Miyamoto Y, Iwai C, Matsuda Y, Hiraoka E, Kanazawa K et al (2009) Delivery may affect arterial elasticity in women. Circ J 73:750–754
28. Manalo-Esrrella P, Barker AE (1967) Histopathologic findings in human aortic media associated with pregnancy. Arch Pathol 83:336–341

29. Loeys BL, Dietz HC, Braverman AC, Callewaert BL, Backer JD, Devereux RC et al (2010) The revised Ghent nosology for the Marfan syndrome. J Med Genet 47:476–485
30. Akutsu K, Morisaki H, Takeshita S, Sakamoto S, Tamori Y, Yoshimuta T et al (2007) Phenotypic heterogeneity of Marfan-like connective tissue disorders associated with mutations in the transforming growth factor-beta receptor genes. Circ J 71:1305–1309
31. Akutsu K, Morisaki H, Okajima T, Yoshimuta T, Tsutsumi Y, Takeshita S et al (2010) Genetic analysis of young adult patients with aortic disease not fulfilling the diagnostic criteria for Marfan syndrome. Circ J 74:990–997
32. Loeys BL, Schwarze U, Holm T et al (2006) Aneurysm syndromes caused by mutations in the TGF-beta receptor. N Engl J Med 355:788–798
33. Loeys BL, Chen J, Neptune ER et al (2005) A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. Nat Genet 37:275–281
34. Malhotra A, Westesson PL (2009) Loeys-Dietz syndrome. Pediatr Radiol 39:1015
35. Williams JA, Loeys BL, Nwakanma LU et al (2007) Early surgical experience with Loeys-Dietz: a new syndrome of aggressive thoracic aortic aneurysm disease. Ann Thorac Surg 83:S757–S763; discussion S785–90
36. Murray ML, Pepin M, Peterson S, Byers PH (2014) Pregnancy-related deaths and complications in women with vascular Ehlers–Danlos syndrome. Genet Med 16:874–880
37. Hovatta O (1999) Pregnancies in women with Turner's syndrome. Ann Med 31:106–110
38. Vincent B (2004) Major vascular anomalies in Turner syndrome. Circulation 110:1694–1700
39. Turner AM (2014) Noonan syndrome. J Paediatr Child Health 50:E14–E20
40. Prendiville TW (2014) Cardiovascular diseases in Noonan syndrome. Arch Dis Child 99:629–634

Congenital Heart Disease

14

Chizuko Aoki-Kamiya

Abstract

Congenital heart disease (CHD) is the most common congenital defect, with an incidence of about 1%. Recent advanced clinical practice concerning CHD has enabled most women with CHD to reach childbearing age, preserving normal daily life. Therefore, the number of pregnancies with CHD is increasing. The various advanced operative methods, including Fontan operation, are widely spread, and the range and severity of CHD in pregnant women are expanding. The clinical management of pregnancies with CHD requires comprehensive knowledge and experience.

Most women with repaired CHD endure pregnancy and delivery, while some have high peripartum mortality and morbidity. Thus, the women with CHD should receive appropriate advice and counselling about pregnancy with specialists, beforehand. Generally, women with cyanotic CHD have higher peripartum maternal and fetal risks than those with acyanotic CHD. The women with high pregnancy risks should be followed up carefully when they get pregnant. A multidisciplinary team, which is composed of trained obstetricians, adult and pediatric cardiologists, anesthesiologists, midwives, and other specialists involved, is necessary for the management of such pregnancies.

Keywords

Congenital heart disease · Pregnancy · Cyanosis · Heart failure · Arrhythmia

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14.1 Overview

The frequency of congenital heart disease (CHD), which is the most common inborn defect, is about 1%. Recent advances in clinical practice related to CHD resulted in a large and growing population of adult CHD who require lifelong cardiac and non-cardiac services. Today, more than 90% of patients with CHD survive into adulthood in Japan [1]. Therefore, many women with CHD desire to bear children, and the number of pregnancies complicated with CHD has been increasing (Fig. 14.1). The range and severity of CHD in such pregnancies and deliveries are also expanding. Because maternal hemodynamics dramatically changes during pregnancy and delivery, maternal and fetal risks are high in some diseases and conditions. Cardiovascular disease is one of the leading causes of maternal death in the world. Therefore, women with CHD should have appropriate preconception advice and counselling with a specialist beforehand (see Chap. 5). Then, when women with high pregnancy risks become pregnant, careful follow-up through antepartum to postpartum by a multidisciplinary team is needed. The review of literatures showed that important cardiac complications such as heart failure and arrythmias were seen in 11% of the pregnancies with CHD. In complex CHD, premature delivery and offspring mortality rates were high, and more children were small for gestational age [2]

14.2 Pregnancy in Each of Congenital Heart Disease

14.2.1 Non-cyanotic Heart Disease

In left-to-right shunt diseases, such as atrial septal defect (ASD), ventricular septal defect (VSD), patent foramen ovale (PFO), and patent ductus arteriosus (PDA), heart murmur becomes louder with a pregnancy-induced increase in circulating

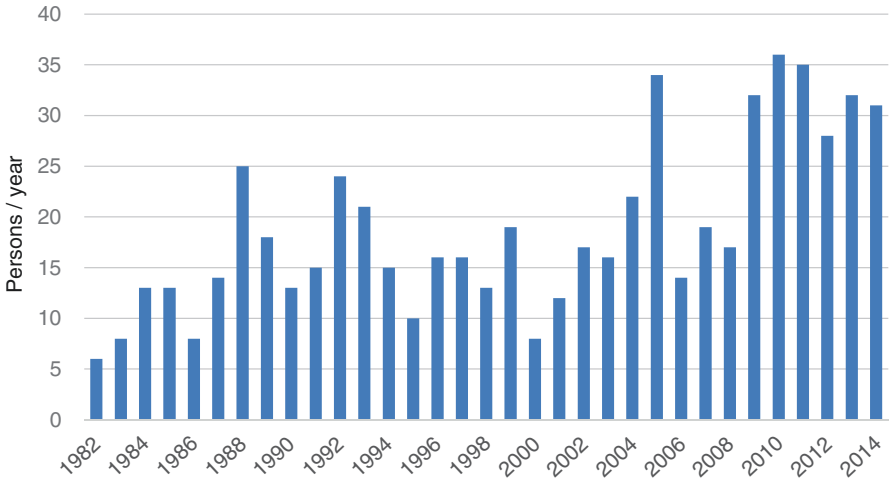

Fig. 14.1 Annual numbers of deliveries complicated with congenital heart disease at the National Cerebral and Cardiovascular Center, Osaka, Japan

blood volume, and the disease may be initially diagnosed in some cases. Even in cases with a large shunt volume, this is balanced with reduction of peripheral vascular resistance, and most cases complete pregnancy and delivery without complication by heart failure (Fig. 14.2). However, when hemorrhage suddenly occurs,

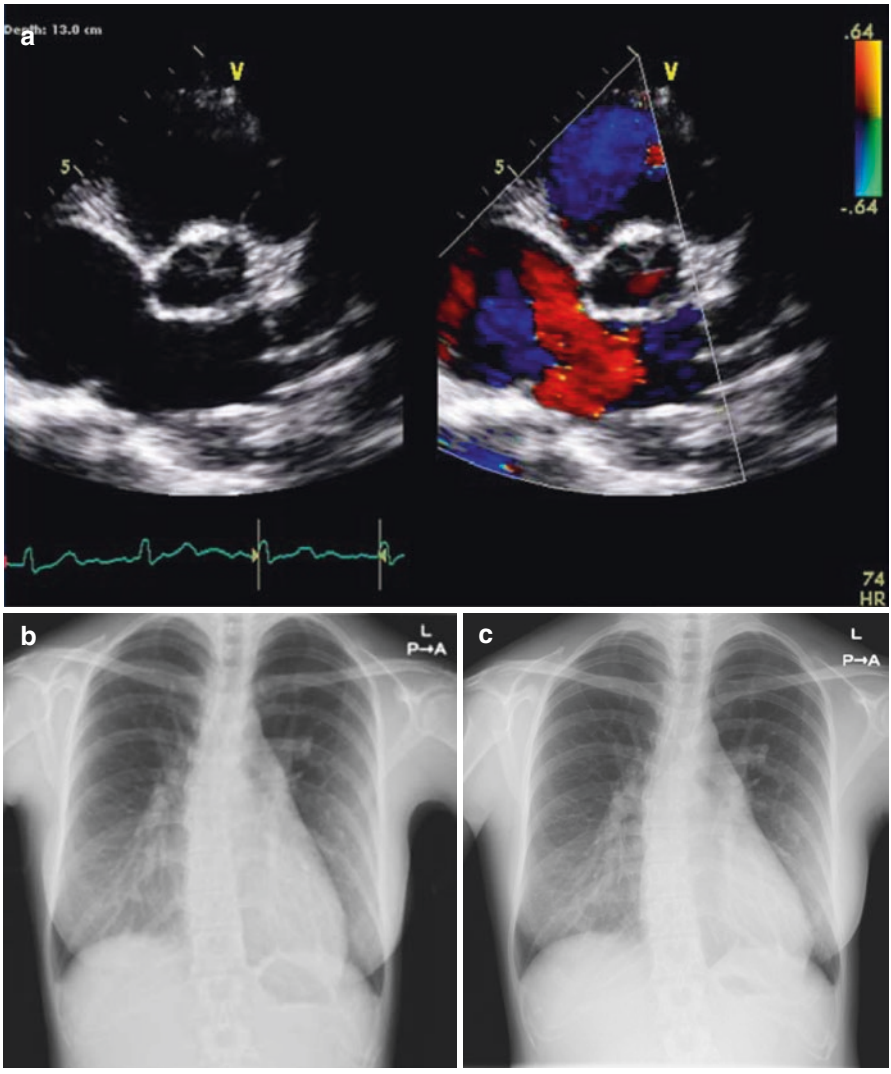

Fig. 14.2 A clinical course of pregnancy complicated with significantly large atrial septal defect. She had rejected an operation for her large atrial septal defect (estimated Qp/Qs > 3 by echocardiography, **a**) and got pregnant. Her chest X-rays showed enlargement of cardiac silhouette due to pregnancy-induced volume extension (**b**, taken before pregnancy; **c**, taken in postpartum). She complained of mild dyspnea 2 days after delivery. She took diuretics for 3 days, and her symptom resolved

shunt blood flow increases due to peripheral vascular constriction and cardiac output decreases, which may cause congestive heart failure, shock, and ventricular fibrillation. Thus, such cases require attention.

ASD, PFO The risk of miscarriage and premature delivery is slightly higher than that in normal pregnancy, and supraventricular arrhythmia and paradoxical embolism may develop concomitantly. Neonatal events occur more frequently in unrepaired ASD than repaired ASD [3], and therefore, it is desirable to perform closure before pregnancy when it is indicated. Cases treated with percutaneous ASD closure during pregnancy have been reported. Otherwise, most cases of unrepaired ASD without heart failure will tolerate pregnancy.

VSD Cases without heart failure in childhood and VSD discovery during pregnancy or those with no indication for surgical treatment have few problems during pregnancy. However, there was a report that the rate of preeclampsia was increased among unrepaired VSD [4]. Cases with significant deviation-induced aortic valve regurgitation are recommended for surgery before pregnancy because this can modify VSD.

Ebstein's Disease The pregnancy risk varies depending on the severity of tricuspid regurgitation, right ventricle (RV) function, and grade of concomitant ASD. Since WPW syndrome is often complicated, supraventricular tachycardia may be observed. Severe cases may have right heart failure, paradoxical embolism, endocarditis, and fetal hypoxemia. In a study of 111 pregnancies in 44 patients with Ebstein's disease, 76% reached delivery, premature delivery occurred in 27%, and CHD was present in 4% of neonates. However, no patients died, and the morbidity of Ebstein's disease was as low as 0.6% [5]. In a Japanese study, maternal and fetal outcomes were generally good, without cardiac failure in patients with NYHA class I prepregnancy [6]. Only two cases gave very early preterm births: one with mechanical tricuspid valve was complicated with an intracerebral hemorrhage, and another had symptomatic chronic heart failure (NYHA II) before pregnancy (Fig. 14.3).

Corrected Transposition of the Great Arteries (cTGA) Pregnancy in women with systemic RV can be poorly tolerated. The increased blood volume during pregnancy may result in heart failure, worsen tricuspid regurgitation, or exacerbate arrhythmia (Fig. 14.4). The pregnancy risk varies depending on the severity of tricuspid regurgitation, RV function, and grade of complications, such as VSD and atrioventricular block. In a study of 60 pregnancies in 22 patients with cTGA, 83% reached delivery, premature delivery before the 30th week occurred in one case, and no neonate had CHD. Excluding one case of heart failure that developed due to atrioventricular valve regurgitation on the systemic circulation side, heart failure and endocarditis developed only in a grand multipara with 12 pregnancies (10 deliveries including twins and 2 miscarriages), and no patient died [7]. However, the

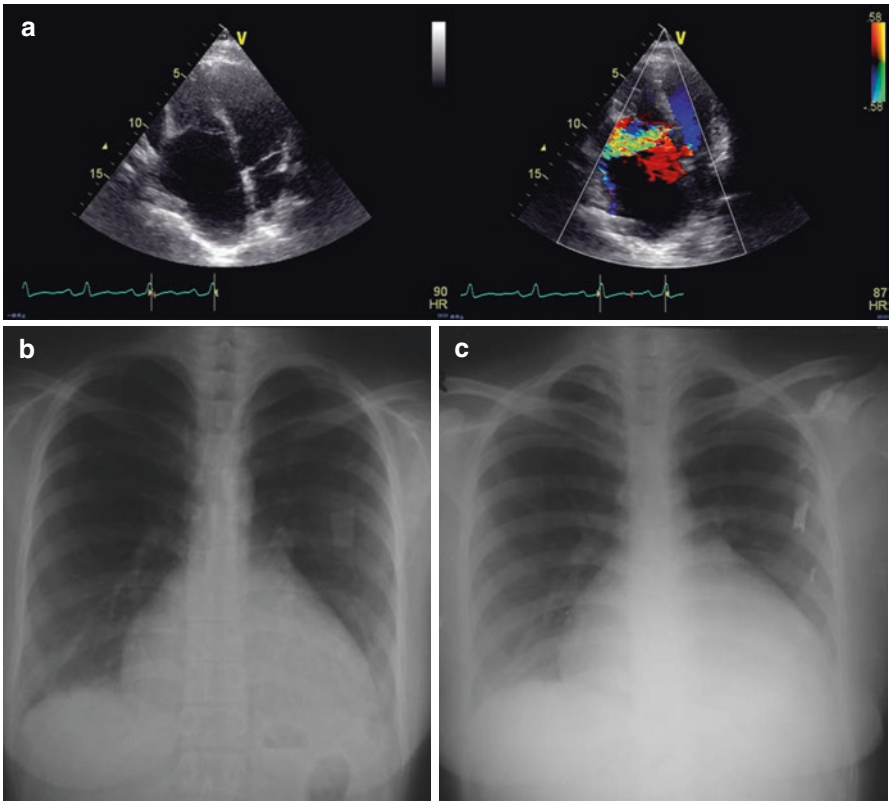

Fig. 14.3 **A clinical course of pregnancy complicated with severe Ebstein's disease**. She was in NYHA class II with small right ventricle and tricuspid regurgitation due to displaced tricuspid valve (**a**) before pregnancy. She was complicated with ventricle tachycardia in 24 weeks of gestation and started on ß-blocker. She became in NYHA class III in 26 weeks of gestation and delivered by Caesarean section. Her chest X-rays are shown as (**b**) taken in early pregnancy and (**c**) taken in 26 weeks of gestation

involvement of pregnancy and delivery in the long-term outcome has not been clarified. As described later, the right heart is more strongly influenced by the loads of pregnancy and delivery, to which attention should be paid in cases with significant atrioventricular valve regurgitation and reduced RV function. There is no published report about a pregnancy after an anatomic repair for cTGA.

After Surgery for Non-cyanotic Heart Disease When repair is favorable, pregnancy and transvaginal delivery are possible, as in normal cases. However, the risk of arrhythmic event due to incision line may be higher than in normal cases (Fig. 14.5). In cases with postoperative residual pulmonary hypertension, the maternal and fetal risks are high.

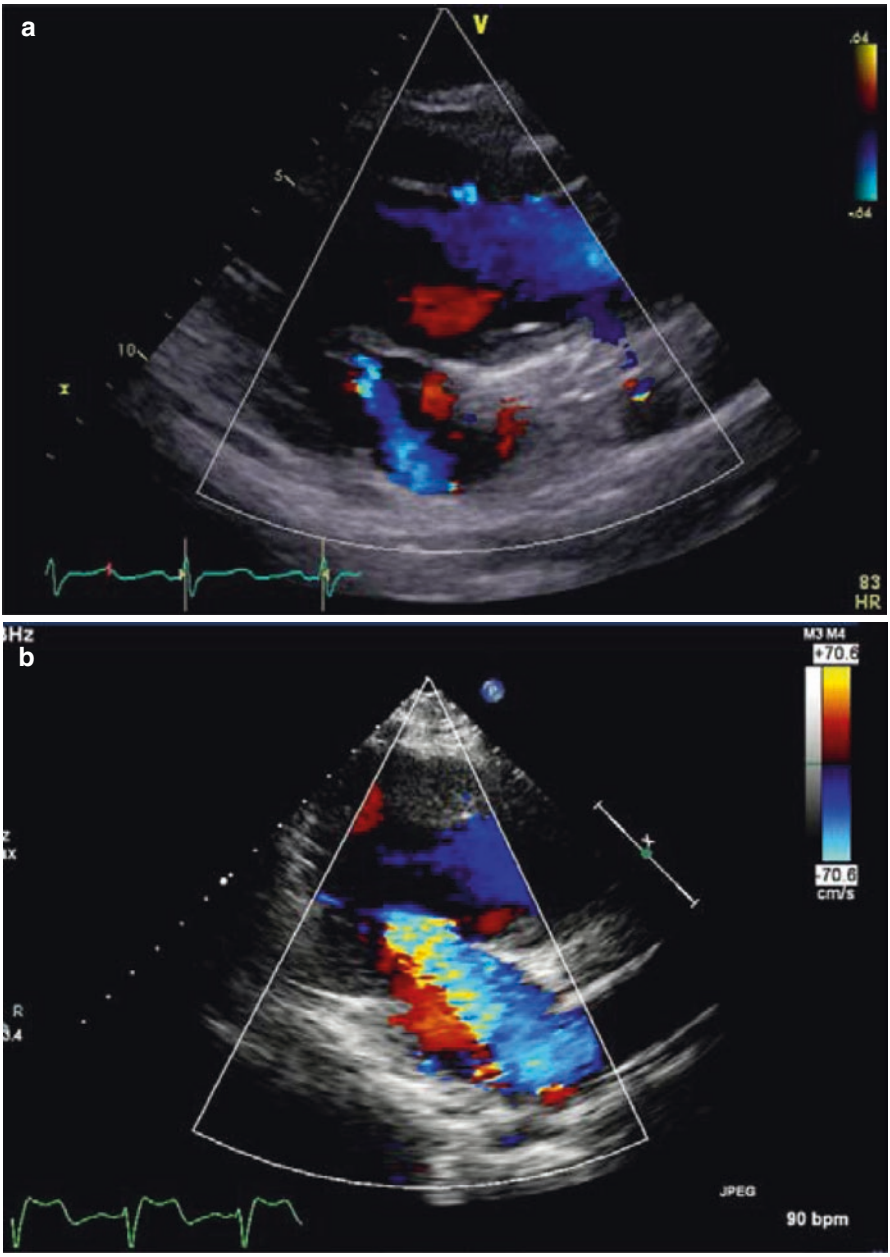

Fig. 14.4 The exacerbated tricuspid regurgitation by pregnancy in a woman with corrected transposition of the great arteries. She had moderate grade of tricuspid regurgitation (TR) before pregnancy (**a**) with taking angiotensin-converting enzyme (ACE) inhibitor. She was stopped ACE inhibitor when she got pregnant. Then, her TR became worsened to severe grade in the middle of her pregnancy (**b**)

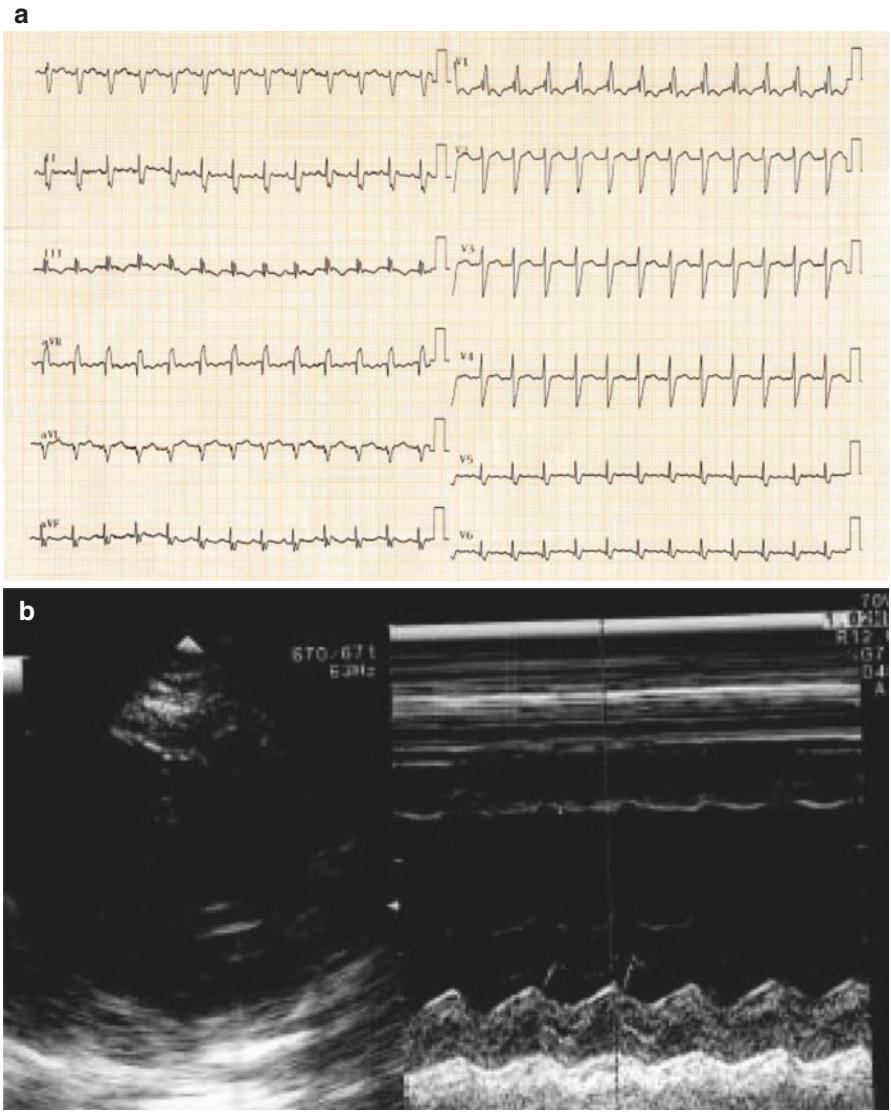

Fig. 14.5 The reduced left ventricular contraction by atrial tachycardia in a postpartum woman with repaired ventricular septal defect. She underwent an operation for ventricular septal defect at 0 year old. Her cardiac function was maintained before and during pregnancy with normal sinus rhythm. After delivery, she complained of shortness of breath and palpitation. Her electrocardiogram showed 153 bpm atrial tachycardia (AT, **a**) and reduced left ventricle contraction (**b**) with pulmonary edema. She was treated with diuretics and catecholamine. After stabilizing pulmonary congestion, she took catheter ablation for her AT

14.2.2 Cyanotic Heart Disease

14.2.2.1 After Surgery for Cyanotic Heart Disease

Even after repair, the pregnancy risk is generally high due to residual and secondary symptoms, compared with that of non-cyanotic heart disease. Thus, ZAHARA score (see Chap. 5), which is the risk assessment of pregnancy with concomitant CHD, is increased by +1 for cyanotic heart disease, regardless of repair.

Tetralogy of Fallot (TOF) Residual VSD, moderate to severe pulmonary arterial valve stenosis and regurgitation, aortic valve regurgitation, concomitant pulmonary hypertension, aortic dilatation (≥40 mm), cardiac hypofunction, and history of tachyarrhythmia have been reported as pregnancy risk factors [8]. In a Japanese study of 40 pregnancies in 25 patients, most of them were well-tolerated pregnancy and delivery, and the mean gestational period was 37.8 weeks [9]. Cardiovascular events were observed in seven pregnancies (18.5%) (arrhythmia, one; heart failure, two; arrhythmia and heart failure, four), and a history of ablation and the baseline cardiothoracic ratio on chest radiography were predictors of adverse cardiac events. Peak plasma brain natriuretic peptide (BNP) level after the second trimester was higher in patients with cardiac events [9].

Transposition of the Great Arteries (TGA) After atrial switch operations, such as Senning and Mustard operations, aggravation of NYHA class, progression of RV dilatation and hypofunction, and an increase in tricuspid regurgitation upon pregnancy occur in some patients, and pregnancy may influence the long-term outcome of heart disease with RV dysfunction [10]. Arrhythmias often become a problem, too. After a Jatene procedure, the pregnancy outcomes seem to go well [11], but cases with severe regurgitation, aortic dilatation, and coronary arterial lesions require careful attention (Fig. 14.6).

After a Fontan Operation Pregnancy and delivery are possible in a case with NYHA classes I–II and favorable cardiac function retaining sinus rhythm, but the miscarriage rate is high up to 40–50%. In a study of 33 pregnancies after a Fontan operation, 15 pregnancies in 14 patients (45%) reached delivery. Complications during pregnancy included supraventricular arrhythmia and heart failure in one case each. The only fetal complication was ASD in one case [12]. In a study of 124 pregnancies in 50 women, 68 (54.8%) resulted in miscarriages, and 53 (42.7%) were live birth but included 4 neonatal deaths [13]. Low maternal oxygen saturations (<85%) were significantly related to miscarriages. There is no consensus on use of anticoagulant and antiplatelet therapies during pregnancy, and further accumulation of cases is required to evaluate the use of this therapy.

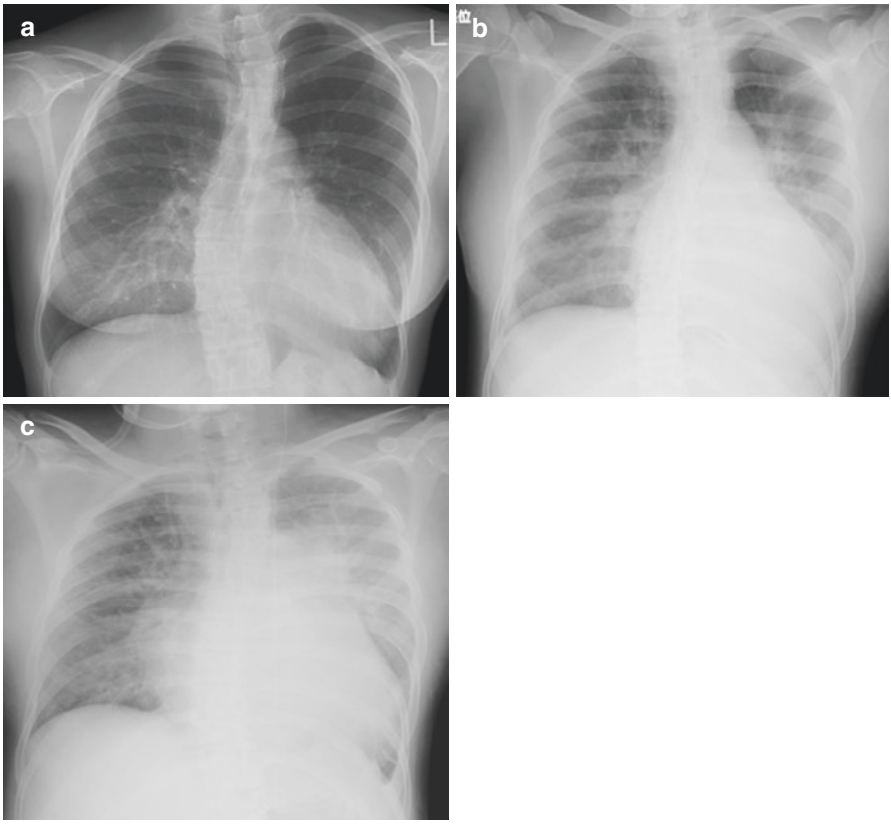

Fig. 14.6 The clinical course of a twin pregnancy in a woman after Jatene operation. She was in NYHA class II before pregnancy and had a twin pregnancy. She had several atrial and ventricular arrhythmic events during pregnancy. Her plasma brain natriuretic peptide (BNP) levels were around 50 pg/mL before and during the first half of pregnancy and then elevated more than 150 pg/mL at 32 weeks of gestation. At the same time, she started to complain of shortness of breath. Her twin babies were diagnosed as intrauterine growth arrest, and she delivered by Caesarean section at 34 weeks of gestation. Her chest X-ray changed from 26 weeks of gestation (**a**) to 33 weeks of gestation (**b**) and 6 hours after delivery (**c**). She was given intravenous administration of diuretics, and her pulmonary edema was resolved

14.2.2.2 Cyanotic Heart Disease Without Pulmonary Hypertension

Somatic vascular resistance decreases during pregnancy, and right to left shunt increases, enhancing cyanosis. The frequency of maternal cardiac complications is high, but many of these are treatable, and the risk of death is low. In contrast, the fetal outcome is poor, and fetal development is strongly inhibited by severe cyanosis [14]. Ability Index, hemoglobin, and arterial oxygen saturation before the

pregnancy were factors related to fetal outcomes. When maternal hemoglobin levels were more than 20 g/dL, the rate of live birth was only 8%. When maternal arterial oxygen saturations were less than 85%, the rate of live birth was only 12%. As described earlier, low maternal oxygen saturations (<85%) in women after Fontan operation significantly related to miscarriages [13].

14.2.3 Congenital Heart Disease with Pulmonary Hypertension

Pulmonary hypertension is one of the cardiovascular conditions with the highest pregnancy risk. Even though pulmonary vasodilators, such as prostacyclin analogues and phosphodiesterase inhibitors, have improved patients' prognosis, maternal risks are still high, and pregnancy is contraindicated in women with pulmonary hypertension. There have been several reports about pregnancies in women with Eisenmenger syndrome, who were treated by pulmonary vasodilators during pregnancy [15, 16]. As the recent review of pregnancy with pulmonary hypertension, the maternal mortality in patients with all kinds of pulmonary hypertension was decreased from 38% between 1978 and 1996 to 16% between 1998 and 2013, but the maternal mortality in the subgroup with congenital heart disease was decreased only from 36% between 1978 and 1996 to 23% between 1998 and 2013 [17]. This indicates that new targeted treatments for pulmonary hypertension are less effective in pregnant patients with congenital heart disease than those with other etiology of pulmonary hypertension. Detail risks of pregnancy with pulmonary hypertension are referred to Chap. 12.

14.2.4 Aortic Disease

Pregnancy causes increased cardiac output and heart rate, and pregnancy-related hormonal changes have been demonstrated to weaken elastic fibers, resulting in degeneration of the aortic tunica media. Therefore, women with aortic disorders such as genetic connective tissue diseases (see Chap. 13) and bicuspid aortic valves have increased risk of aortic dilatation and dissection during pregnancy and postpartum [18].

Aortic Coarctation Many patients are hypertensive before pregnancy, and the risk of hypertensive disorders of pregnancy (HDP) is higher than that in the general population, especially in cases with significant stenosis (pressure gradient ≥20 mmHg) [19]. Since cerebral aneurysm often develops concomitantly, evaluation before pregnancy is preferable.

In the series of 15 pregnancies in 9 Japanese women with aortic coarctation, prepregnancy Doppler-measured pressure gradient ≥20 mmHg and a left

ventricular mass index ≥95 g/m^2 were significant risk factors for HDP. The left ventricular end-diastolic diameters at the first and the third trimesters, the left ventricular end-systolic diameters at the first trimester, and the left ventricular ejection fraction at the third trimester were also significantly higher in the pregnancies with HDP [20].

Bicuspid Aortic Valve Development of aortic dissection during pregnancy in patients with bicuspid aortic valve (BAV) has been reported [21, 22]. Recently, most international reference centers proposed a proactive approach for BAV patients with a maximum ascending aortic/root diameter of 45 mm since the risk of dissection/rupture raises significantly with an aneurysm diameter >50 mm. In asymptomatic women with a well-functioning BAV, elective repair is recommended for diameters ≥45–50 mm, in case of planned pregnancy [23]. The use of β-blocker during pregnancy may be considered in the case with significantly dilated aorta (Fig. 14.7).

Aortic Dilatation Associated with CHD (Aortopathy) Aortic dissection can occur in patients with TOF and hypoplastic left heart, but no case of dissection during pregnancy has been reported. There are no specific surgical indications, but criteria for surgery include ≤50 mm for cases with rapid dilatation (>1 cm/year) after repair of TOF, familial medical history of dissection, and moderate or severe aortic valve regurgitation and ≥55 mm after repair of TOF not meeting the criteria described above [24].

14.3 Influence of Pregnancy

In pregnancy after repair of TOF, right cardiac dilatation progresses upon pregnancy and delivery. In our institution, indexes of the LV system did not change from before to after pregnancy and delivery, but the RV diameter significantly dilated at 6 months to 1 year after delivery, compared with the diameter before pregnancy [9]. In a study in which the patient background was matched with regard to CHD and echocardiography indexes were compared between delivery and nondelivery groups, RV dilatation was noted in patients who became pregnant after repair of TOF [25]. In a study of the RV volume before and after pregnancy, RV dilatation markedly increased after delivery in cases in which the dilatation had advanced before pregnancy [26]. Figure 14.8 shows cases in which RV dilatation progressed after delivery. Since significant changes of RV dysfunction are observed after delivery, even after Senning and Mustard operations, treatment of RV dilatation and function may be necessary for pregnancy with CHD.

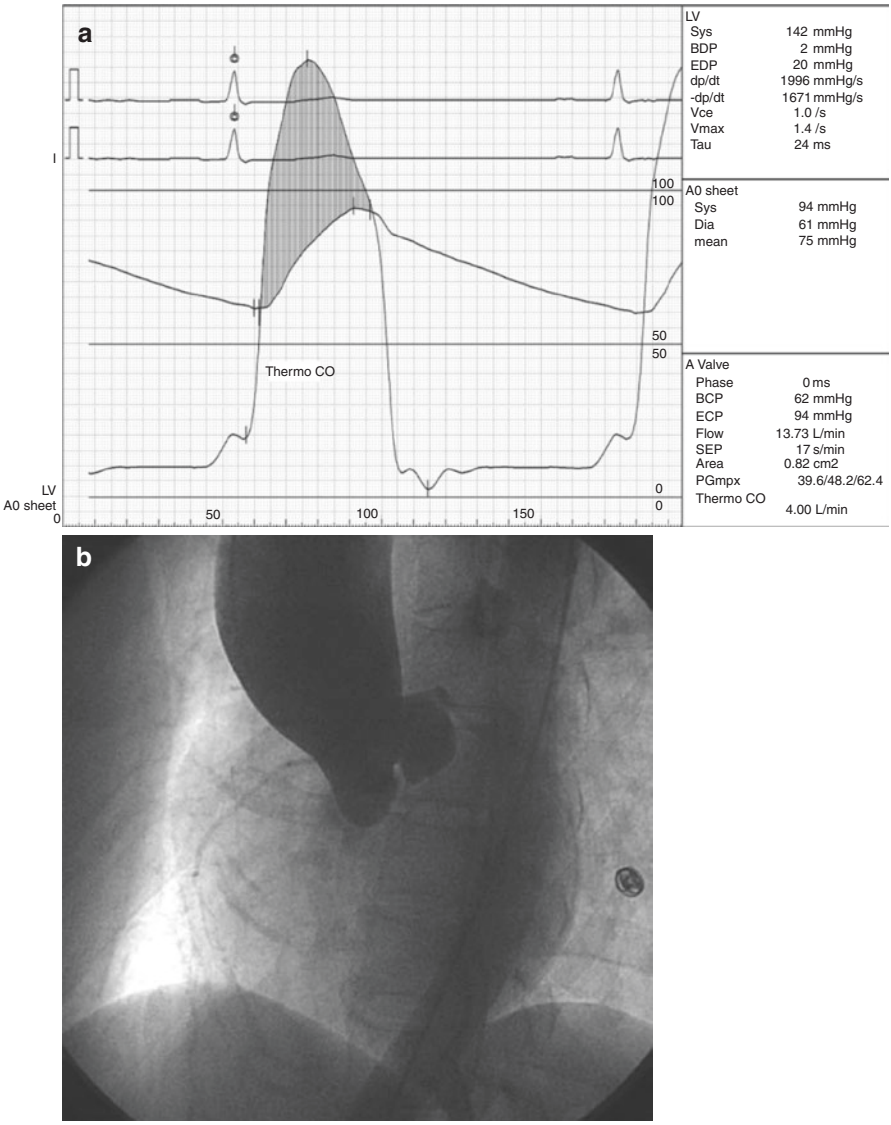

Fig. 14.7 A pregnant woman with bicuspid aortic valve and dilated ascending aorta. An asymptomatic woman with bicuspid aortic valve stenosis (mean pressure gradient; 40 mmHg, **a**) and dilated ascending aorta (42 mm, **b**) at catheterization study. She started to complain of mild chest discomfort on effort in her third trimester and was treated by β-blocker. No aortic event occurred in peripartum

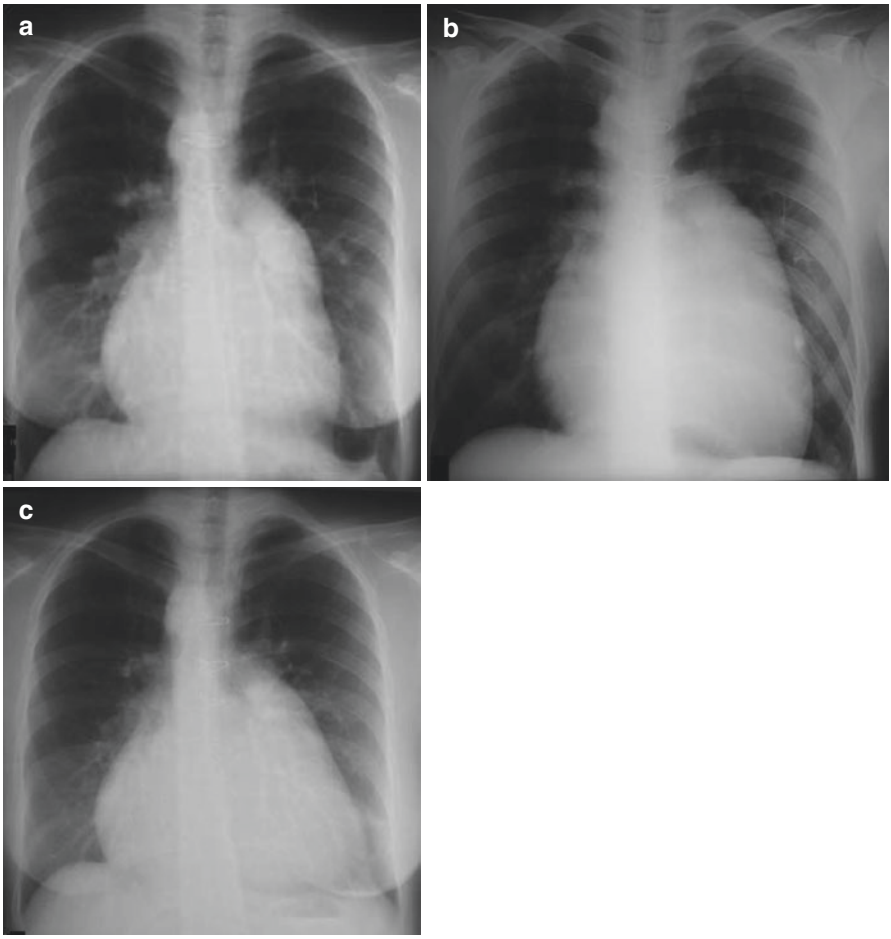

Fig. 14.8 A woman with repaired tetralogy of Fallot in whom pregnancy had an impact on the progression of enlarged right heart. She had severe pulmonary regurgitation and atrial tachycardia before pregnancy. Her chest X-ray showed more enlarged heart after pregnancy (**a**, before pregnancy; **b**, right before delivery; **c**, 1 year after delivery)

14.4 Heredity and Fetal Echocardiography

The causes of CHD are explained due to chromosomal aberration, a single gene aberration, environmental factors, and multifactorial inheritance of unknown cause in 8, 2, 5, and 85% of cases, respectively. Offspring of women with CHD are at increased risk of CHD. The risk of recurrence of CHD was reported from 2.9 to 7.0% in previous studies [27–29]. The accuracy of fetal echocardiography has recently improved, and CHD is diagnosed in the fetal period in 50–60% of cases. Therefore, screening by fetal echocardiography is useful for mothers with CHD.

References

1. Shiina Y, Toyoda T, Kawasoe Y et al (2011) Prevalence of adult patients with congenital heart disease in Japan. Int J Cardiol 146:13–16
2. Drenthen W, Pieper PG, Roos-Hesselink JW et al (2007) Outcome of pregnancy in women with congenital heart disease. J Am Coll Cardiol 49(24):2303–2311
3. Yap SC, Drenthen W, Meijboom FJ et al (2009) Comparison of pregnancy outcomes in women with repaired versus unrepaired atrial septal defect. BJOG 116:1593–1601
4. Yap SC, Drenthen W, Pieper PG et al (2010) Pregnancy outcome in women with repaired versus unrepaired isolated ventricular septal defect. BJOG 117:683–689
5. Connolly HM, Warnes CA (1994) Ebstein's anomaly: outcome of pregnancy. J Am Coll Cardiol 23:1194–1198
6. Katsuragi S, Kamiya C, Yamanaka K et al (2013) Risk factors for maternal and fetal outcome in pregnancy complicated by Ebstein anomaly. Am J Obstet Gynecol 209(452):e1–e6
7. Connolly HM, Grogan M, Warnes CA (1999) Pregnancy among women with congenitally corrected transposition of great arteries. J Am Coll Cardiol 33:1692–1695
8. Veldtman GR, Connolly HM, Grogan M et al (2004) Outcomes of pregnancy in women with tetralogy of Fallot. J Am Coll Cardiol 44:174–180
9. Kamiya CA, Iwamiya T, Neki R et al (2012) Outcome of pregnancy and effects on the right heart in women with repaired tetralogy of fallot. Circ J 76:957–963
10. Guédès A, Mercier LA, Leduc L et al (2004) Impact of pregnancy on the systemic right ventricle after a Mustard operation for transposition of the great arteries. J Am Coll Cardiol 44:433–437
11. Tobler D, Fernandes SM, Wald RM et al (2010) Pregnancy outcomes in women with transposition of the great arteries and arterial switch operation. Am J Cardiol 106:417–420
12. Canobbio MM, Mair DD, van der Velde M et al (1996) Pregnancy outcomes after the Fontan repair. J Am Coll Cardiol 28:763–767
13. Cauldwell M, Steer PJ, Bonner S et al (2018) Retrospective UK multicentre study of the pregnancy outcomes of women with a Fontan repair. BMJ 104:401–406
14. Presbitero P, Somerville J, Stone S et al (1994) Pregnancy in cyanotic congenital heart disease. Outcome of mother and fetus. Circulation 89:2673–2676
15. Lacassie HJ, Germain AM, Valde's G et al (2004) Management of Eisenmenger syndrome in pregnancy with sildenafil and L-arginine. Obstet Gynecol 103:1118–1120
16. Daimon A, Kamiya CA, Iwanaga N et al (2017) Management of pulmonary vasodilator therapy in three pregnancies with pulmonary arterial hypertension. J Obstet Gynaecol Res 43:935–938
17. Pieper PG, Lameijer H, Hoendermis ES (2014) Pregnancy and pulmonary hypertension. Clin Obst Gynaecol 28:579–591
18. Donnelly RT, Pinto NM, Kocolas I et al (2012) The immediate and long-term impact of pregnancy on aortic growth rate and mortality in women with Marfan syndrome. J Am Coll Cardiol 60:224–229
19. Beauchesne LM, Connolly HM, Ammash NM et al (2001) Coarctation of the aorta: outcome of pregnancy. J Am Coll Cardiol 38:1728–1733
20. Sato H, Kamiya CA, Sawada M et al (2017) Changes in echocardiographic parameters and hypertensive disorders in pregnancies of women with aortic coarctation. Pregnancy Hypertens 10:46–50
21. Immer FF, Bansi AG, Immer-Bansi AS et al (2003) Aortic dissection in pregnancy: analysis of risk factors and outcome. Ann Thorac Surg 76:309–314
22. Yang Z, Yang S, Wang F et al (2016) Acute aortic dissection in pregnant women. Gen Thorac Cardiovasc Surg 64:283–285
23. Etz CD, Misfeld M, Borger MA et al (2012) Current indications for surgical repair in patients with bicuspid aortic valve and ascending aortic ectasia. Cardiol Res Pract 2012:1. https://doi.org/10.1155/2012/313879

24. Dearani JA, Burkhart HM, Stulak JM et al (2009) Management of the aortic root in adult patients with conotruncal anomalies. Semin Thorac Cardiovac Surg Pediatr Card Surg Annu 12:122–129
25. Uebing A, Arvanitis P, Li W et al (2010) Effect of pregnancy on clinical status and ventricular function in women with heart disease. Int J Cardiol 139:50–59
26. Egidy Assenza G, Cassater D, Landzberg M et al (2013) The effects of pregnancy on right ventricular remodeling in women with repaired tetralogy of Fallot. Int J Cardiol 168:1847–1852
27. Gill HK, Splitt M, Sharland GK et al (2003) Patterns of recurrence of congenital heart disease: an analysis of 6,640 consecutive pregnancies evaluated by detailed fetal echocardiography. J Am Coll Cardiol 42:923–929
28. Siu SC, Sermer M, Colman JM et al (2001) Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation 104:515–521
29. Burn J, Brennan P, Little J et al (1998) Recurrence risks in offspring of adults with major heart defects: results from first cohort of British collaborative study. Lancet 351:311–316

Pregnancy After Cardiac Valve Replacement

15

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Abstract

Pregnancy after heart valve replacement is highly risky for both the mother and child due to the aggravation of maternal heart function and the adverse effects of some drugs, such as anticoagulant or antiarrhythmic drugs.

The recent decrease in the prevalence of rheumatic heart disease among young women has also decreased the use of mechanical heart valves. Developments in cardiac surgery have replaced mechanical heart valves with bioprosthetic heart valves. However, advances in cardiac surgery have even enabled women with mechanical heart valves to survive for a long term. For such women, long-term management of coagulability is absolutely necessary. The management of pregnancy after mechanical valve replacement is most difficult due to this need for anticoagulant therapy.

Keywords

Pregnancy after cardiac valve replacement · Mechanical valve · Bioprosthetic valve · Ross procedure

15.1 Pregnancy After Valve Surgery

Congenital or acquired valvular heart disease can be repaired using autologous, bioprosthetic, or mechanical valves. These valves have many postoperative problems in terms of durability, deformation, and susceptibility to infection. The sequelae due to the graft valve differ according to the valve type, hemodynamics, and replacement site.

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In recent years, due to the decrease in the number of children with rheumatic fever, the frequency of cardiac valve replacement in the young has also decreased. In addition, due to advances in surgical treatment, bioprosthetic valve replacement tends to be selected at ages allowing for pregnancy and delivery on the premise that valve re-replacement may be performed [1]. At present, pregnant females who have undergone mechanical valve replacement are encountered less frequently. However, recent advances in treatment techniques have facilitated the long-term survival of patients with complicated congenital heart disease, and management of patients after valve replacement showing conditions that have not been encountered previously is necessary. The American College of Obstetricians and Gynecologists (ACOG) classifies the risk of each cardiovascular disease based on the maternal mortality [2]. The risk is less than 1% (Group 1) after bioprosthetic valve replacement and 5–15% (Group 2) after mechanical valve replacement.

For young females who have undergone valve replacement, adequate prepregnancy counseling is necessary. Some of the drugs prescribed in nonpregnant women are contraindicated during pregnancy. Thus, planned pregnancies are necessary after evaluation including any changes in drugs after conception. In the graft valve, valve thrombosis, stenosis, and regurgitation can occur, and cardiac failure or arrhythmia due to hemodynamic changes can develop during pregnancy. Clarification of the valve function before pregnancy and hemodynamics during the prepregnancy period allows the accurate evaluation of changes post-conception and early treatment [3].

15.2 After Bioprosthetic Valve Replacement

The main advantage of bioprosthetic valves is that no anticoagulation therapy is necessary. However, bioprosthetic valves are inferior to mechanical valves in terms of durability and require replacement when they deteriorate. Bioprosthetic valves used in the left heart system generally require replacement after 10–15 years. Therefore, it is desirable that females become pregnant and deliver children, while they are managed with bioprosthetic valves, and undergo replacement with mechanical valves thereafter. Bioprosthetic valves are highly safe when the underlying disease is stable and controlled, but prevention of infective endocarditis is necessary when invasive surgical procedures are necessary. Although pregnancy has been suggested to have no influence on the durability of bioprosthetic valves, patients have been reported who required valve replacement earlier than usual, and opinions remain divided [4, 5]. Even after prosthetic valve replacement, serial changes in the cardiac function, hemodynamics, and valve function should be evaluated throughout pregnancy and the postpartum period, using methods such as echocardiography. Valve deterioration can cause valve stenosis and regurgitation, but generally valve stenosis progresses gradually, while regurgitation progresses acutely as it is caused by the rupture of calcified areas [6].

15.3 After Mechanical Valve Replacement

Pregnancy after mechanical valve replacement is associated with markedly increased maternal and fetal risks, such as maternal death, cardiac failure, arrhythmia, and infective endocarditis [7]. We sometimes select abortion or the induction of early delivery to mitigate or balance these risks. Anticoagulation therapy during pregnancy after mechanical valve replacement brings both the maternal risk of hemorrhage such as intracranial hemorrhage and intrauterine hematoma and the fetal risk of congenital anomalies, miscarriage, and early death [8]. Inadequate anticoagulation therapy can cause fatal maternal thromboembolism or valve insufficiency. While the durable period of prosthetic valves is long (≥20 years), and the likelihood of requiring valve replacement is low, continuous anticoagulation therapy is necessary [9]. Pregnancy after mechanical valve replacement requires strict adjustment of the anticoagulant dose and careful consideration of the possible development of complications associated with anticoagulation therapy. During pregnancy, since changes to a physiologically hypercoagulable state occur, more elaborate anticoagulation regimens are necessary compared with those during the nonpregnancy period.

Warfarin can be administered orally, and its dose can be more readily adjusted than heparin. However, since warfarin is teratogenic and is associated with a high abortion rate, it is recommended that the drug used in anticoagulation therapy should be changed from warfarin to heparin during the first trimester of pregnancy [10, 11]. The anticoagulant regimens in pregnant women with mechanical heart valves recommended by the American College of Chest Physicians (ACCP) are shown in Table 15.1 [12]. The treatment range with heparin is narrow, and control by percutaneous injection alone is often difficult. Even anticoagulation therapy by percutaneous injection of dose-adjusted unfractionated heparin or low-molecular-weight heparin can lead to thrombosis [13]. There have been no studies comparing the subcutaneous injection and continuous intravenous infusion of unfractionated heparin. We have reported that the continuous intravenous infusion of

Table 15.1 Recommended anticoagulant regimens in pregnant women with mechanical heart valves

Adjusted-dose bid LMWH throughout pregnancy, with doses adjusted to achieve the manufacturer's peak anti-Xa LMWH 4 h postsubcutaneous injection (Grade 1A)
Adjusted-dose UFH throughout pregnancy administered subcutaneously every 12 h in doses adjusted to keep the mid-interval aPTT at least twice control or attain an anti-Xa heparin level of 0.35–0.70 units/mL (Grade 1A)
UFH or LMWH (as above) until the 13th week with substitution by vitamin K antagonists until close to delivery when UFH or LMWH is resumed (Grade 1A)
For women judged to be at very high risk of thromboembolism in whom concerns exist about the efficacy and safety of UFH or LMWH as dosed above (e.g., older-generation prosthesis in the mitral position or history of thromboembolism), vitamin K antagonists throughout pregnancy with replacement by UFH or LMWH (as above) close to delivery (Grade 2C)

GRADE Grades of Recommendations, Assessment, Development, and Evaluation, *aPTT* activated partial thromboplastin time, *LMWH* low-molecular-weight heparin, *UFH* unfractionated heparin

unfractionated heparin could reduce the incidence of maternal thrombosis. Fetal intracranial hemorrhage during anticoagulation therapy with warfarin in the second trimester has been reported, and the fetal toxicity of warfarin includes embryopathy and other conditions [14]. In recent years, studies on anticoagulation therapy among Japanese have shown that anticoagulation without complications can be achieved at a lower dose than that shown by studies in Western countries [15–18]. With respect to the fetal toxicity of warfarin, a warfarin dose ≤5 mg was reported to have no influences on the fetus. However, due to ethnic differences in sensitivity to anticoagulants, further studies are necessary [19].

In recent years, mechanical valves with a decreased risk of thrombus formation have been developed, and anticoagulation has been shown to be possible with oral Xa inhibitors at lower than the conventional dose. Their use during pregnancy is anticipated [13].

In patients who are managed with warfarin until near delivery, warfarin is changed to heparin. Since the half-life of warfarin in the blood is long (about 40 h), this drug change is in preparation for a sudden delivery; thus, heparin is discontinued immediately before delivery. Since the half-life of heparin is 2 h, it is discontinued 6 h before delivery if it is being administered by continuous intravenous infusion. For unexpected early delivery, APTT is measured before delivery, and if sustained effects of heparin are observed, protamine sulfate is administered to neutralize the heparin. Heparin administration is resumed 6 h after vaginal delivery and 12 h after caesarean delivery. Since warfarin requires 2–3 days to achieve effective anticoagulation, oral warfarin administration is initiated when the absence of hemorrhagic complications is confirmed under heparin administration.

While trace amounts of warfarin pass into breast milk, no anticoagulation effects have been reported in infants breastfed by mothers using warfarin [20].

15.4 After Aortic Valve Replacement with an Autograft (Ross Procedure)

The Ross procedure involves the replacement of a diseased aortic valve with an autologous pulmonary artery valve. Prosthetic grafts, such as a homograft, are used to replace the excised pulmonary valve. Due to the simultaneous replacement of two valves, high levels of skill are necessary, and the invasiveness of the procedure is increased. However, this procedure has many advantages. Due to the use of an autograft, operation is possible even in children with a small annulus. Since the valve itself grows, reoperation is not necessary. In addition, there is no need for anticoagulation therapy [21].

Morimoto et al. compared the outcome of pregnancy between young adult females after the Ross procedure and those after bioprosthetic valve replacement. They reported that there were no significant differences in the outcome of pregnancy between the two groups and few females required reoperation after the Ross procedure, thus concluding that the Ross procedure is optimal among aortic valve replacement techniques for females who wish to have children [22]. Another study

showed no adverse influences of pregnancy after the Ross procedure on the pulmonary autograft valve in the aortic valve position or the graft valve in the pulmonary artery valve position and that no maternal complications occurred during or after pregnancy [23].

References

1. North RA, Sadler L, Stewart AW, McCowan LM, Kerr AR, White HD (1999) Long-term survival and valve-related complications in young women with cardiac valve replacements. Circulation 99:2669–2676
2. American College of Obstetricians and Gynecologists: Cardiac diseases in pregnancy. Technical Bulletin No 168, 1992
3. Elkayam U, Bitar F (2005) Valvular heart disease and pregnancy: part II: prosthetic valves. J Am Coll Cardiol 46:403–410
4. Cleuziou J, Hörer J, Kaemmerer H, Teodorowicz A, Kasnar-Samprec J, Schreiber C, Lange R (2010) Pregnancy does not accelerate biological valve degeneration. Int J Cardiol 145(3):418–421. https://doi.org/10.1016/j.ijcard.2010.04.095. Epub 2010 Jun 3
5. Hanania G, Thomas D, Michel PL, Garbarz E, Age C, Millaire A, Acar J (1994) Pregnancy and prosthetic heart valves: a French cooperative retrospective study of 155 cases. Eur Heart J 15(12):1651–1658
6. Taylor J (2011) The first ESC guidelines on the management of cardiovascular diseases during pregnancy. Eur Heart J 32:3055–3056
7. Chan WS, Anand S, Ginsberg JS (2000) Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. Arch Intern Med 160:191–196
8. Nassar AH, Hobeika EM, Abd Essamad HM, Taher A, Khalil AM, Usta IM (2004) Pregnancy outcome in women with prosthetic heart valves. Am J Obstet Gynecol 191:1009–1013
9. Greer IA (2002) Exploring the role of low-molecular-weight heparins in pregnancy. Semin Thromb Hemost 28(Suppl 3):25–31
10. Hall JG, Pauli RM, Wilson KM (1980) Maternal and fetal sequelae of anticoagulation during pregnancy. Am J Med 68:122–140
11. Ayhan A, Yapar EG, Yuce K, Kisnisci HA, Nazli N, Ozmen F (1991) Pregnancy and its complications after cardiac valve replacement. Int J Gynaecol Obstet 35:117–122
12. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO, American College of Chest Physicians (2012) VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141(2 Suppl):e691S–e736S. https://doi.org/10.1378/chest.11-2300
13. Kaneko T, Aranki SF (2013) Anticoagulation for prosthetic valves. Thrombosis 2013:346752. https://doi.org/10.1155/2013/346752. Epub 2013 Nov 4. Review
14. Kawamata K (2007) Risk and pregnancy outcome in women with prosthetic mechanical heart valve replacement. Circ J 71:211–213
15. Inoue H, Nozawa T, Okumura K, Iwasa A, Lee JD, Shimizu A et al (2004) Attitudes of Japanese cardiologists toward anticoagulation for non- valvular atrial fibrillation and reasons for its underuse. Circ J 68:417–421
16. Nozawa T, Inoue H, Iwasa A, Okumura K, Jong-dae L, Shimizu A et al (2004) Effects of anticoagulation intensity on hemostatic markers in patients with non-valvular atrial fibrillation. Circ J 68:29–34
17. Uetsuka Y, Hosoda S, Kasanuki H, Aosaki M, Murasaki K, Ooki K et al (2000) Optimal therapeutic range for oral anticoagulants in Japanese patients with prosthetic heart valves: a preliminary report from a single institution using conversion from thrombotest to PT-INR. Heart Vessel 15:124–128

18. Yamaguchi T (2000) Optimal intensity of warfarin therapy for secondary prevention of stroke in patients with nonvalvular atrial fibrillation: a multicenter, prospective, randomized trial: Japanese Nonvalvular Atrial Fibrillation-Embolism Secondary Prevention Cooperative Study Group. Stroke 31:817–821
19. Vitale N, De Feo M, De Santo LS, Pollice A, Tedesco N, Cotrufo M (1999) Dose-dependent fetal complications of warfarin in pregnant women with mechanical heart valves. J Am Coll Cardiol 33:1637–1641
20. McKenna R, Cole ER, Vasan U (1983) Is warfarin sodium contraindicated in the lactating mother? J Pediatr 103(2):325–327
21. El-Hamamsy I, Eryigit Z, Stevens LM et al (2010) Long-term outcomes after autograft versus homograft aortic root replacement in adults with aortic valve disease: a randomised controlled trial. Lancet 376:524–531
22. Morimoto K, Hoashi T, Kagisaki K et al (2015) Impact of Ross operation on outcome in young female adult patients wanting to have children. Circ J 79(9):1976–1983
23. Dore A, Somerville J (1997) Pregnancy in patients with pulmonary autograft valve replacement. Eur Heart J 18:1659–1662

Arrhythmia

16

Takekazu Miyoshi

Abstract

Arrhythmias are by far the most common complication in adults with structural heart disease and complicate a substantial number of pregnancies. Most arrhythmias are benign, but therapy should be initiated for pregnant women with severe symptoms or hemodynamically unstable arrhythmias. Arrhythmias are also an important trigger for the occurrence of heart failure. All antiarrhythmic drugs undergo placental transfer to varying degrees, and there is potential for fetal effects. Therefore, the lowest effective dose of the medication should be chosen. Since atrial flutter/fibrillation, atrial tachycardia, ventricular tachycardia, and complete atrioventricular block may cause significant hemodynamic changes that may seriously affect the mother and fetus, appropriate diagnosis and emergency treatment are commonly required. Catheter ablation in pregnant women should be undertaken in a situation in which reasonable medication is ineffective. Pregnant women who present with unstable ventricular arrhythmias and at high risk for sudden cardiac death during pregnancy may be candidates for implantable cardioverter-defibrillator implantation. Since cardiac arrest is more common in the postpartum period compared with during pregnancy and labor, temporary use of a wearable cardioverter defibrillator in the postpartum period may be suitable for patients at higher risk of ventricular arrhythmias and long QT syndrome. This chapter reviews different types of arrhythmias and gives an overview of the current treatment strategies.

Keywords

Antiarrhythmic drug · Arrhythmia · Bradycardia · Implantable cardioverter defibrillator · Pregnancy · Tachycardia

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16.1 Arrhythmias and Pregnancy

The incidence of cardiac arrhythmias is higher in pregnancy, and all forms of arrhythmia and structural heart disease may be encountered. Pregnancy may trigger exacerbations of pre-existing arrhythmias, or arrhythmias may manifest for the first time. Palpitation, dizziness, breathlessness, chest pain, and pre-syncope suggest premature contractions and tachyarrhythmias, which are more common during pregnancy. The precise mechanism of increased arrhythmia burden during pregnancy is unclear; however, it is probably due to a combination of hemodynamic, hormonal, and autonomic changes. Circulating blood volume increases more rapidly after 20 weeks of gestation, and the blood volume at 30 weeks of gestation is 40–45% greater than the nonpregnancy volume. Cardiac output is also increased to an average of 8.7 L/min in the third trimester. This is the result of a 35% increase in stroke volume and a 15% increase in heart rate. The increase in plasma volume causes stretching of atrial and ventricular myocytes, and this may result in early after depolarizations, shortened refractoriness, slowed conduction, and spatial dispersion through activation of stretch-activated ion channels [1, 2]. A larger heart can also potentially sustain reentry more easily because of an increase in path length of potential reentrant circuits. The increase in heart rate during pregnancy, seen predominantly in the third trimester, may also predispose to arrhythmia, as a high resting heart rate has been associated with markers of arrhythmogenesis [3]. Hormonal and autonomic changes may also contribute to arrhythmogenesis. Estradiol and progesterone have been shown to be proarrhythmic in animal studies and in case reports of pregnant patients with arrhythmias [4]. In addition, estrogen increases the number of adrenergic receptors in the myocardium, and adrenergic responsiveness seems to be increased in pregnancy [5].

Fortunately, most maternal arrhythmias are benign, but therapy should be initiated for pregnant women with severe symptoms or hemodynamically unstable arrhythmias [6]. Althogh multiple antiarrhythmic drugs are available for use in pregnancy, data are limited and further prospective, and registry studies are required to evaluate the safety of these agents. If possible, therapy should be limited to the first trimester, and drugs with the longest safety record should be used first. In a case of refractory or life-threatening arrhythmia, higher-risk intervention should be considered.

16.2 Arrhythmias and Congenital Heart Disease

Arrhythmias are the most common reason for hospital admission in patients with congenital heart disease (CHD) [7]. Complex cardiac anatomy and the presence of scars due to past surgical procedures are the primary causes of arrhythmia. Furthermore, intrinsic conduction abnormalities may be present, such as Wolff-Parkinson-White (WPW) syndrome in Ebstein's anomaly, which affects 20% of patients [8]. Intra-atrial reentrant tachycardia (IART) mostly affects patients with atrial septal defect, tetralogy of Fallot (TOF), transposition of the great arteries

(TGA) after a Mustard or Senning operation, and single ventricle physiology after a Fontan operation [9, 10]. Atrial fibrillation (AF) occurs more frequently in congenital anomalies of the mitral valve, aortic valve stenosis, and single ventricle and constitutes 25–30% of arrhythmias in patients with CHD. Ventricular tachycardia (VT) mainly affects patients with TOF, with the 10-year risk of sudden cardiac death reaching 2% in the first 20–25 years after corrective surgery [11]. In this regard, identification of high-risk patients for primary prevention is imperative. A risk score has been proposed for predicting appropriate implantable cardioverter-defibrillator (ICD) discharges, including palliative shunt, inducible sustained VT, QRS duration >180 ms, nonsustained VT, ventriculotomy incision, and left ventricular end-diastolic pressure >12 mmHg [12].

Bradycardia is common in patients with heterotaxy syndrome with single ventricle and is relatively common following previous surgical procedures, such as Mustard, Senning, and Fontan operations. Congenital atrioventricular (AV) block is associated with heterotaxy syndrome and corrected TGA. The prognosis of congenital bradycardia with CHD is still poor due to dilated cardiomyopathy, heart failure, and sudden cardiac death [13]. In general, the overall incidence of sudden cardiac death in CHD is low (0.09% per year), but significantly higher than in the general population [14].

16.3 Management of Arrhythmias in Pregnancy

In general, the therapeutic approach to arrhythmias in pregnancy is similar to that in the nonpregnant patient. Hyperthyroidism should be excluded, and other systemic disorders that can result in arrhythmia, such as pulmonary embolism, should be considered. Treatment of arrhythmias should be reserved for significant symptoms or arrhythmias resulting in hemodynamic compromise and risk to the mother and fetus. Depending on the underlying cardiac condition and hemodynamic stability, a rate or rhythm control strategy should be chosen, although rhythm control is often preferred over rate control in pregnant patients with CHD and new-onset arrhythmias. Patients with a known history of uncontrolled arrhythmia should undergo treatment before becoming pregnant, when possible.

16.3.1 Tachyarrhythmias

16.3.1.1 Supraventricular Tachycardia

Supraventricular tachycardia (SVT) is the most common sustained arrhythmia encountered during pregnancy, with a prevalence of 24 per 100,000 hospital admissions [15], and 20% of patients with pre-existing SVT will experience symptomatic exacerbations during pregnancy [16]. In women without CHD, paroxysmal SVT is most commonly due to atrioventricular nodal reentrant tachycardia (AVNRT) followed by atrioventricular reciprocating tachycardia (AVRT) [17]. It is unclear whether pregnancy increases the risk of the first onset of SVT. Patients with

pre-existing SVT may experience exacerbations during pregnancy. SVT is usually well tolerated but can result in hemodynamic deterioration in patients with CHD and result in impaired fetal blood flow [18].

16.3.1.2 Atrioventricular Nodal Reentrant Tachycardia

AVNRT in pregnant patients should initially be managed with avoidance of precipitating factors and use of vagal maneuvers to terminate acute episodes of the arrhythmia. In hemodynamically stable patients, adenosine is the first-line agent and terminates 90% of paroxysmal SVT [19]. Due to the short half-life (1–2 s), adenosine is unlikely to reach the fetal circulation. If adenosine is ineffective, intravenous metoprolol or propranolol should be used. Verapamil is considered a third-line agent [16]. For patients with frequent symptomatic episodes, metoprolol or verapamil can be used for the prevention of SVT. Although digoxin is safe in pregnancy, it is often ineffective alone but has been used in combination with a beta-blocker for AVNRT. Sotalol or flecainide may be used in cases with significant symptoms that do not respond to atrioventricular nodal blocking agents. In rare cases, drug-refractory, hemodynamically significant AVNRT during pregnancy has been treated with catheter ablation with low radiation exposure to the fetus. For long-term therapy, beta-blockers, calcium channel blockers, digoxin, or flecainide may be used in patients with concealed accessory pathways. For patients with WPW syndrome, verapamil or digoxin should not be used because of the risk of rapid accessory pathway conduction during AF. Beta-blockers can be used cautiously in patients with WPW syndrome, especially if the accessory pathway is not capable of rapid conduction [16].

16.3.1.3 Atrial Tachycardia

Atrial tachycardia is relatively rare during pregnancy, but pregnancy may contribute to its initiation and maintenance [20]. Atrial tachycardia is often persistent and refractory to medical therapy and even cardioversion, and tachycardia-induced cardiomyopathy may be present. For acute treatment, adenosine should be used first as this is diagnostic and occasionally successful in terminating the arrhythmia. Combination therapies of beta-blockers, calcium channel blockers, or digoxin can be used for rate control. If these agents fail to control the arrhythmia, sotalol or flecainide may be considered. In cases of incessant, symptomatic atrial tachycardia, catheter ablation has been performed safely [21].

16.3.1.4 Atrial Fibrillation and Atrial Flutter

AF and atrial flutter (AFL) are rare during pregnancy, with a prevalence of 2 in 100,000 hospital admissions [15]. Atypical AFL is the most common arrhythmia caused by atrial scars, whereas AF is particularly rare in pregnant women without CHD. Among women with previously diagnosed AF, more than half will have symptomatic episodes during pregnancy [22]. Hemodynamically unstable episodes of AF or AFL should be treated with electric cardioversion. In stable patients, flecainide and ibutilide have been used safely in case reports to convert AF in pregnancy; however, there is no broad experience with chemical

cardioversion [23, 24]. For most patients, rate control with beta-blockers, calcium channel blockers, or digoxin may be considered as acute therapy. In patients where rate control fails or in those with poorly tolerated episodes of AF, a rhythm control strategy with antiarrhythmic drugs is reasonable. Sotalol or flecainide is the preferred antiarrhythmic drug in this setting.

Systemic anticoagulation is recommended for pregnant patients with AF and AFL who have risk factors for thromboembolism. The benefit of aspirin in lower-risk patients with AF is controversial. Given the potential of teratogenicity, warfarin should not be used in the first trimester. Warfarin is also not recommended for prophylactic use, even in the second and third trimesters, because of the potential risk of fetal cerebral hemorrhage and demise. Thus, low-molecular-weight heparin or unfractionated heparin is preferred, especially in the first trimester and the last month of pregnancy [25]. Heparin administration is also recommended for patients with persistent episodes in whom electric cardioversion is planned. The benefit and risk for fetus of direct oral anticoagulants during pregnancy are not clear yet.

16.3.1.5 Ventricular Tachycardia

VT and ventricular fibrillation (VF) are rare during pregnancy, with a prevalence of 2 in 100,000 hospital admissions [15]. When ventricular arrhythmias do occur, it is usually in the setting of CHD and a history of VT, and the risk of recurrent VT in such patients is as high as 27% [26]. VT has been described during pregnancy in a variety of cardiomyopathies, including hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy [27–29]. Ischemic cardiomyopathy is uncommon; however, myocardial infarction complicated by VT/VF with or without coronary artery disease has been observed [30]. Patients with CHD are at relatively high risk for VT, with a prevalence of 4.5–15.9 per 1000 pregnancies [31]. In patients without CHD who develop symptoms of heart failure in the last month of pregnancy or in the months after delivery, peripartum cardiomyopathy should be considered [32, 33]. Cases of peripartum cardiomyopathy presenting with VT during pregnancy have been reported, but the etiology remains unknown.

In pregnant patients with CHD, treatment of VT should be tailored to the underlying cardiac condition. For acute management of VT, electric cardioversion should be performed in the setting of hemodynamic instability. In hemodynamically tolerated VT, pharmacological cardioversion with lidocaine should be tried first. Procainamide or quinidine may then be used if lidocaine is ineffective. Given the risk of fetal harm, amiodarone should only be used in life-threatening situations when other therapies have failed [34]. Chronic antiarrhythmic drug therapy is often warranted in patients with VT and CHD because of the risk of hemodynamic compromise and sudden death. A beta-blocker (metoprolol or propranolol) is indicated for most patients. Sotalol may be considered if beta-blockers are ineffective. Mexiletine and quinidine are reasonable alternative agents, but class IC agents should not be used because they are associated with increased mortality in nonpregnant patients with CHD [35].

Recurrent idiopathic VT is typically hemodynamically stable and associated with a good prognosis [36]. This condition may present for the first time during pregnancy and is often catecholamine-sensitive. Treatment of outflow tract VT with cardioselective beta-blockers in pregnant patients is usually effective [37]. Fascicular VT is typically verapamil-sensitive, and verapamil can be used for both acute termination and prevention of recurrence [38]. Therefore, beta-blockers or verapamil are recommended as first-line agents for idiopathic VT. Sotalol or flecainide may be considered in patients with significant symptoms that do not respond to beta-blocker therapy.

16.3.2 Bradyarrhythmias

Sinus node dysfunction and atrioventricular block are rare in pregnancy, especially in structurally normal hearts [15]. Congenital complete AV block is occasionally diagnosed for the first time during pregnancy. Asymptomatic patients with complete AV block without other evidence of conduction disease or CHD often have a good prognosis and can be managed expectantly. In the past, temporary pacing during labor and delivery was advocated for all patients with complete AV block because of potential bradycardia and syncope with Valsalva [39]. However, more recent studies suggest that temporary pacing is unnecessary in stable patients with complete AV block [40]. Pregnant patients with symptomatic or hemodynamically unstable bradyarrhythmias may require permanent pacing. Although bradycardias are generally well tolerable during pregnancy and labor, additional caution is required in the postpartum period.

16.3.3 Long QT Syndrome

Long QT syndrome is an inherited ion channel disorder that has the potential to cause VT and torsades de pointes, resulting in syncope, cardiac arrest, or sudden death. It is uncertain whether women with long QT syndrome are at increased risk for ventricular arrhythmias during pregnancy [41]. The relative tachycardia and increased estrogen during pregnancy may serve to shorten the QT interval and be protective for pregnant women with long QT syndrome. Cardiac arrest is more common in the postpartum period compared with before or during pregnancy. There is increased risk in the postpartum period that is potentially related to a decrease in heart rate, stress, and altered sleep patterns. A retrospective study of 422 women with long QT syndrome found that probands were significantly more likely to have syncope, aborted cardiac arrest, or sudden death in the 40-week postpartum interval compared with the 40-week prepregnancy period (23.4% vs. 3.8%). In addition, beta-blocker therapy was associated with decreased risk of cardiac events before pregnancy, during pregnancy, and postpartum [34]. Propranolol is the preferred agent, as metoprolol may not be as effective in long QT syndrome 1 and 2 [42, 43]. Recently, nadolol was reported as the only beta-blocker associated with a significant risk reduction in patients with long QT syndrome 2 [44].

16.3.4 Antiarrhythmic Drugs

There is a clinical consensus on the efficacy and safety of antiarrhythmic drugs in pregnancy (Table 16.1), despite the lack of availability of a randomized control study. The US Food and Drug Administration (FDA) adopted a rule eliminating this system in favor of a more descriptive approach in which labeling is expected to include an overview of the risks of the particular drug during pregnancy, along with pertinent data [45]. Most antiarrhythmic drugs are recognized as that 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 the use of the drug in pregnant women despite potential risks. All antiarrhythmic drugs undergo placental transfer to varying degrees, and there is potential for fetal effects. It is important to choose the lowest effective dose of the medication. The fetus is most sensitive to teratogenicity in the first trimester. Thus, medication should be limited during the first trimester, and drugs with the longest safety record should be used first. Medications of modest risk that have long been effective in controlling significant arrhythmias should be continued in most clinical settings during this period, as the stability of the patient may supersede the potential risks of the medication [46, 47]. During the second and third trimesters, the effects of antiarrhythmic drugs on fetal growth and development, fetal arrhythmias, and uterine contractility become a concern. However, several antiarrhythmic drugs are known to be safe and effective as transplacental treatment of fetal tachyarrhythmias (see Chap. 18 "Fetal Arrhythmia"). Digoxin, sotalol, or flecainide is usually used as first-line fetal therapy [48].

The Vaughan-Williams system classifies antiarrhythmic drugs based on their primary mechanisms of action (Table 16.1). Class I agents are sodium channel blockers that prolong repolarization and increase the risk of torsades de pointes. While using such drugs, fetal monitoring with magnetocardiography may be considered to evaluate the presence of underlying prolonged QT intervals in fetuses [49]. Class I agents are divided into subcategories such as IA, IB, and IC, according to the effects of sodium channel blocking. Quinidine, procainamide, and disopyramide are class IA agents historically used for treatment of AF/AFL and VT. Disopyramide should be avoided during pregnancy due to the potential increased risk for preterm labor. Lidocaine and mexiletine are class IB agents used for treatment of maternal and fetal VT. Mexiletine is associated with fetal growth restriction (FGR) and neonatal transient hypoglycemia. Flecainide and propafenone are class IC agents used for the treatment of SVT and VT. These drugs should only be used in patients without CHD or coronary artery disease. Flecainide is preferred over propafenone during pregnancy, because propafenone also has beta-blocking properties and experience is more limited than flecainide.

Beta-blockers are class II agents and the first choice for most arrhythmias. The FDA classifies beta-blockers as pregnancy category C drugs during the first and second trimesters and as pregnancy category D drugs, meaning there is evidence of risk, during the third trimester. Beta-blockers are associated with FGR and bradycardia and neonatal hypoglycemia and jaundice [50]. In addition, beta-blockers are thought to have little effect on the unstressed fetus, but adverse effects may become

Table 16.1 Antiarrhythmic drugs in pregnancy

Vaughan-Williams class	Drug	Risk category[a]	Maternal or obstetrical adverse event	Fetal adverse event	Fetal therapy	Neonatal adverse event
IA	Quinidine	△	QTc prolongation	QTc prolongation	Yes	Thrombocytopenia, Ototoxicity, QTc prolongation
	Procainamide	△	QTc prolongation	QTc prolongation		Drug-induced lupus, QTc prolongation
	Disopyramide	△	QTc prolongation	QTc prolongation		Hypoglycemia, Preterm labor, QTc prolongation
IB	Lidocaine	○	Hypotension, CNS AE		Yes	CNS AE
	Mexiletine	△	Hypotension, CNS AE	FGR	Yes	CNS AE, Hypoglycemia, low Apgar score
IC	Flecainide, Propafenone	△	Bradycardia, AV block, QTc prolongation	Bradycardia, AV block, QTc prolongation	Yes	CNS AE, Bradycardia, QTc prolongation
II	Propranolol, Metoprolol	△	Hypotension, Uterine contractions, Bradycardia	FGR, Bradycardia	Yes	Hypoglycemia, Jaundice, Apnea, Bradycardia
	Atenolol	△	Hypotension, Uterine contractions, Bradycardia	FGR, Bradycardia		Hypoglycemia, Jaundice, Apnea, Bradycardia
	Pindolol	○	Hypotension, Uterine contractions, Bradycardia	FGR, Bradycardia		Hypoglycemia, Jaundice, Apnea, Bradycardia

Vaughan-Williams class	Drug	Risk category[a]	Maternal or obstetrical adverse event	Fetal adverse event	Fetal therapy	Neonatal adverse event
III	Sotalol	○	Bradycardia, AV block, QTc prolongation	Bradycardia, AV block, QTc prolongation	Yes	Bradycardia, AV block, QTc prolongation
	Amiodarone	▲	Bradycardia, AV block, QTc prolongation	Hypothyroidism, FGR, Bradycardia, AV block, QTc prolongation	Yes	Hypothyroidism, Thrombocytopenia, Neurodevelopmental concerns, Bradycardia, AV block, QTc prolongation
	Dofetilide, Ibutilide	△		Proarrhythmia		
	Dronedarone	×		Vascular and limb abnormalities, Cleft palate		
IV	Verapamil, Diltiazem	△	Hypotension, Bradycardia, AV block	Bradycardia, AV block		Jaundice, Seizure activity, Bradycardia, AV block
N/A	Adenosine	△	Hypotension, Dyspnea, Bradycardia			
	Digoxin	△	Nausea/vomiting, Bradycardia, AV block	Bradycardia, AV block	Yes	Bradycardia, AV block
	Magnesium sulfate	▲	CNS AE, loss of patellar reflex		Yes	Low calcium levels, Bone problems

[a]Risk category in pregnancy is based on FDA risk information. ◎ controlled studies show no risk, ○ no evidence of risk in studies, △ risk cannot be ruled out, ▲ positive evidence of risk, and × contraindicated in pregnancy

AV atrioventricular, *FDA* Food and Drug Administration, *FGR* fetal growth restriction, *CNS* central nervous system, *AE* adverse effect, *TdP* torsades de pointes

apparent during fetal distress because these drugs impair the fetal response to distress [51]. The adverse effect of atenolol appears to be more pronounced in women receiving the drug earlier in pregnancy and continuing the drug for a longer duration [52], whereas a controlled study using metoprolol after the first trimester did not show FGR [53]. Therefore, atenolol may be switched to metoprolol or other beta-blockers because of the slightly increased risks associated with atenolol.

Class III agents are potassium channel blockers. Sotalol, amiodarone, dofetilide, ibutilide, and dronedarone are used for the treatment of SVT and VT. Sotalol also has beta-blocking properties. Amiodarone has sodium channel, calcium channel, and beta-blocking properties, and it causes fetal and neonatal transient hypothyroidism in up to half of cases [54, 55]. Amiodarone should be considered when treatment for life-threatening arrhythmias is required and other antiarrhythmic drugs have failed [34]. Dronedarone is not recommended during pregnancy due to potential teratogenicity. Class IV agents are calcium channel blockers, which are usually used for the treatment of hypertension. Verapamil and diltiazem are used for the treatment of AF/AFL and SVT. Verapamil is preferred over diltiazem due to extensive experience with this drug during pregnancy.

16.3.5 Intervention for Arrhythmias During Pregnancy

16.3.5.1 Electric Cardioversion

Electric cardioversion is a reasonable option at all stages of pregnancy when arrhythmias are associated with hemodynamic instability. This procedure can be considered electively for drug-refractory arrhythmias, and cardioversion does not compromise blood flow to the fetus [56]. In addition, because only a small amount of energy reaches the fetus, the risk of inducing fetal arrhythmias is small [47]. In later stages of pregnancy, there is a theoretical risk of initiating preterm labor. There are case reports of emergency Cesarean delivery because of fetal arrhythmias after cardioversion, and fetal monitoring is advised [57].

16.3.5.2 Catheter Ablation in Pregnancy

There are few studies on catheter ablation in the pregnant patient. In general, this option should only be undertaken in a situation where reasonable medical therapy is ineffective, and the potential risks to the mother and fetus are outweighed by the expected benefit. Potential additional risks of catheter ablation in a pregnant patient versus a nonpregnant patient include fetal radiation exposure and fetal compromise in the event of maternal hemodynamic instability. In addition, the gravid uterus may play a role in difficult patient positioning, as well as present challenges in performance of pericardiocentesis and resuscitation in the event of a complication. If procedures are performed after 20 weeks of gestation, placing a wedge beneath the patient for left lateral uterine displacement is recommended. Radiation exposure to the fetus should be minimized, particularly in early pregnancy during organogenesis and neuronal development. From implantation through 8 weeks of gestation, the threshold dose for fetal abnormalities or mental retardation rises from 100 to

250 mGy [58]. A reasonable threshold for concern of fetal exposure is 50 mGy, as exposure to this dose has not been associated with fetal anomalies or pregnancy loss [59]. Abdominal shielding should be routinely used in pregnancy.

16.3.5.3 Implantable Cardioverter Defibrillators and Pregnancy

Pregnant patients who present with unstable ventricular arrhythmias and at high risk for sudden cardiac death during pregnancy may be candidates for an implantable cardioverter defibrillator (ICD). ICDs can be successfully implanted during pregnancy with little fluoroscopy, and some have used no fluoroscopy with echocardiographic guidance [60]. However, one must be certain of the indication for the device and that all other alternatives have been explored because of potential risks such as maternal hemodynamic instability. Regarding the presence of an ICD during pregnancy, little information is available. Natale et al. reported a multicenter retrospective analysis of 44 pregnant women with ICDs, 42 of whom had abdominal generators [61]. Local complications such as implant site pain and generator migration occurred in 3. Eleven (25%) women received ≥1 shock without direct ill effects on the pregnancy. Pregnancy was not associated with an increase in ICD-related complications or ICD shocks. We also found that pregnancy did not increase the risk of an ICD-related complication under appropriate management [62]. No patient received discharges or shocks from the ICD during pregnancy; however, 1 of 6 mothers received an ICD shock after delivery. Additional caution may be required in the postpartum period, as well as during pregnancy and labor. It remains uncertain whether an ICD should be on or off during delivery. Recurrence of VT decreases placental perfusion due to maternal hypotension and could be dangerous for the fetus. In contrast, ICD shocks are a concern for the safety of the fetus, although the amount of energy transferred to the uterus is very small and the fetal heart has a high fibrillatory threshold. Based on these considerations, we have recently changed our policy to leave the device turned on during vaginal delivery or Cesarean section, with the proviso that electrocautery is not used. Because elevated heart rate during labor may cause inappropriate ICD shock, a multidisciplinary approach involving specialists in maternal fetal medicine, cardiology, and anesthesiology is needed for total management during labor and delivery for a pregnant woman with an ICD. This management needs to be designed specifically to meet these needs at each hospital.

A wearable cardioverter defibrillator (WCD) is a vestlike device worn under the clothing that continuously monitors heart rhythm and automatically delivers an electric shock when VF is detected. This device has been approved by the US FDA for cardiac patients with a transient high risk for VF, such as those awaiting cardiac transplantation, those at very high risk after a recent myocardial infarction or an invasive cardiac procedure, or those requiring temporary removal of an infected implanted defibrillator for antibiotic therapy. A WCD serves its purpose well as a temporary measure for up to 5 or 6 months, at which time a permanent ICD can be provided for the few patients in whom there has not been sufficient improvement. There are quite limited data on the use of a WCD for patients with peripartum cardiomyopathy and left ventricular noncompaction during pregnancy or after birth [63, 64]. A WCD is an

alternative approach to protection against sudden death if a pregnant woman is at risk for malignant arrhythmias and an ICD is either unsuitable or a decision on use of an ICD has not been made. VT, VF, and long QT syndrome are higher risks in the postpartum period, rather than during pregnancy and labor. Therefore, temporary use of a WCD in the postpartum period may be suitable for these conditions.

References

1. Franz MR, Cima R, Wang D, Profitt D, Kurz R (1992) Electrophysiological effects of myocardial stretch and mechanical determinants of stretch-activated arrhythmias. Circulation 86:968–978
2. Ninio DM, Saint DA (2008) The role of stretch-activated channels in atrial fibrillation and the impact of intracellular acidosis. Prog Biophys Mol Biol 97:401–416
3. Soliman EZ, Elsalam MA, Li Y (2010) The relationship between high resting heart rate and ventricular arrhythmogenesis in patients referred to ambulatory 24 h electrocardiographic recording. Europace 12:261–265
4. Odening KE, Choi BR, Liu GX, Hartmann K, Ziv O, Chaves L, Schofield L, Centracchio J, Zehender M, Peng X, Brunner M, Koren G (2012) Estradiol promotes sudden cardiac death in transgenic long QT type 2 rabbits while progesterone is protective. Heart Rhythm 9:823–832
5. Roberts JM, Insel PA, Goldfien A (1981) Regulation of myometrial adrenoreceptors and adrenergic response by sex steroids. Mol Pharmacol 20:52–58
6. Enriquez AD, Economy KE, Tedrow UB (2014) Contemporary management of arrhythmias during pregnancy. Circ Arrhythm Electrophysiol 7:961–967
7. Opotowsky AR, Siddiqi OK, Webb GD (2009) Trends in hospitalizations for adults with congenital heart disease in the U.S. J Am Coll Cardiol 28(54):460–467
8. Walsh EP, Cecchin F (2007) Arrhythmias in adult patients with congenital heart disease. Circulation 30(115):534–545
9. Triedman JK (2002) Arrhythmias in adults with congenital heart disease. Heart 87:383–389
10. Bhatt AB, Foster E, Kuehl K, Alpert J, Brabeck S, Crumb S, Davidson WR Jr, Earing MG, Ghoshhajra BB, Karamlou T, Mital S, Ting J, Tseng ZH, American Heart Association Council on Clinical Cardiology (2015) Congenital heart disease in the older adult: a scientific statement from the American Heart Association. Circulation 26(131):1884–1931
11. Silka MJ, Bar-Cohen Y (2012) A contemporary assessment of the risk for sudden cardiac death in patients with congenital heart disease. Pediatr Cardiol 33:452–460
12. Khairy P, Harris L, Landzberg MJ, Viswanathan S, Barlow A, Gatzoulis MA, Fernandes SM, Beauchesne L, Therrien J, Chetaille P, Gordon E, Vonder Muhll I, Cecchin F (2008) Implantable cardioverter-defibrillators in tetralogy of Fallot. Circulation 22(117):363–370
13. Miyoshi T, Maeno Y, Sago H, Inamura N, Yasukouchi S, Kawataki M, Horigome H, Yoda H, Taketazu M, Shozu M, Nii M, Kato H, Hagiwara A, Omoto A, Shimizu W, Shiraishi I, Sakaguchi H, Nishimura K, Nakai M, Ueda K, Katsuragi S, Ikeda T (2015) Fetal bradyarrhythmia associated with congenital heart defects - nationwide survey in Japan. Circ J 79:854–861
14. Koyak Z, Harris L, de Groot JR, Silversides CK, Oechslin EN, Bouma BJ, Budts W, Zwinderman AH, Van Gelder IC, Mulder BJ (2012) Sudden cardiac death in adult congenital heart disease. Circulation 126(16):1944–1954
15. Li JM, Nguyen C, Joglar JA, Hamdan MH, Page RL (2008) Frequency and outcome of arrhythmias complicating admission during pregnancy: experience from a high-volume and ethnically-diverse obstetric service. Clin Cardiol 31:538–541
16. Blomström-Lundqvist C, Scheinman MM, Aliot EM, Alpert JS, Calkins H, Camm AJ, Campbell WB, Haines DE, Kuck KH, Lerman BB, Miller DD, Shaeffer CW Jr, Stevenson

WG, Tomaselli GF, Antman EM, Smith SC Jr, Alpert JS, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Hiratzka LF, Hunt SA, Jacobs AK, Russell RO Jr, Priori SG, Blanc JJ, Budaj A, Burgos EF, Cowie M, Deckers JW, Garcia MA, Klein WW, Lekakis J, Lindahl B, Mazzotta G, Morais JC, Oto A, Smiseth O, Trappe HJ, American College of Cardiology, American Heart Association Task Force on Practice Guidelines, European Society of Cardiology Committee for Practice Guidelines, Writing Committee to Develop Guidelines for the Management of Patients With Supraventricular Arrhythmias (2003) ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients with Supraventricular Arrhythmias). Circulation 108:1871–1909

17. Lee SH, Chen SA, Wu TJ, Chiang CE, Cheng CC, Tai CT, Chiou CW, Ueng KC, Chang MS (1995) Effects of pregnancy on first onset and symptoms of paroxysmal supraventricular tachycardia. Am J Cardiol 76:675–678
18. Peleg D, Orvieto R, Ferber A, Ben-Rafael Z (1998) Maternal supraventricular tachycardia recorded as apparent fetal heart rate in a case of fetal demise. Acta Obstet Gynecol Scand 77:786–787
19. Elkayam U, Goodwin TM (1995) Adenosine therapy for supraventricular tachycardia during pregnancy. Am J Cardiol 75:521–523
20. Doig JC, McComb JM, Reid DS (1992) Incessant atrial tachycardia accelerated by pregnancy. Br Heart J 67:266–268
21. Ferguson JD, Helms A, Mangrum JM, DiMarco JP (2011) Ablation of incessant left atrial tachycardia without fluoroscopy in a pregnant woman. J Cardiovasc Electrophysiol 22: 346–349
22. European Heart Rhythm Association, European Association for Cardio-Thoracic Surgery, Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH, ESC Committee for Practice Guidelines (2010) Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace 12:1360–1420
23. Burkart TA, Kron J, Miles WM, Conti JB, Gonzalez MD (2007) Successful termination of atrial flutter by ibutilide during pregnancy. Pacing Clin Electrophysiol 30:283–286
24. Kockova R, Kocka V, Kiernan T, Fahy GJ (2007) Ibutilide-induced cardioversion of atrial fibrillation during pregnancy. J Cardiovasc Electrophysiol 18:545–547
25. Konishi H, Miyoshi T, Neki R, Fukuda T, Ishibashi-Ueda H, Ogo T, Nakanishi N, Yoshimatsu J (2015) Intrapartum temporary inferior vena cava filters are rarely indicated in pregnant women with deep venous thromboses. J Vasc Surg Venous Lymphat Disord 3:370–375
26. Silversides CK, Harris L, Haberer K, Sermer M, Colman JM, Siu SC (2006) Recurrence rates of arrhythmias during pregnancy in women with previous tachyarrhythmia and impact on fetal and neonatal outcomes. Am J Cardiol 97:1206–1212
27. Autore C, Conte MR, Piccininno M, Bernabò P, Bonfiglio G, Bruzzi P, Spirito P (2002) Risk associated with pregnancy in hypertrophic cardiomyopathy. J Am Coll Cardiol 40:1864–1869
28. Tanaka H, Kamiya C, Katsuragi S, Tanaka K, Miyoshi T, Tsuritani M, Yoshida M, Iwanaga N, Neki R, Yoshimatsu J, Ikeda T (2014) Cardiovascular events in pregnancy with hypertrophic cardiomyopathy. Circ J 78:2501–2506
29. Bauce B, Daliento L, Frigo G, Russo G, Nava A (2006) Pregnancy in women with arrhythmogenic right ventricular cardiomyopathy/dysplasia. Eur J Obstet Gynecol Reprod Biol 127:186–189
30. Hankins GD, Wendel GD Jr, Leveno KJ, Stoneham J (1985) Myocardial infarction during pregnancy: a review. Obstet Gynecol 65:139–146

31. Tateno S, Niwa K, Nakazawa M, Akagi T, Shinohara T, Yasuda T, Study Group for Arrhythmia Late after Surgery for Congenital Heart Disease (ALTAS-CHD) (2003) Arrhythmia and conduction disturbances in patients with congenital heart disease during pregnancy: multicenter study. Circ J 67:992–997
32. Kamiya CA, Yoshimatsu J, Ikeda T (2016) Peripartum cardiomyopathy from a genetic perspective. Circ J 25(80):1684–1688
33. Ware JS, Li J, Mazaika E, Yasso CM, DeSouza T, Cappola TP, Tsai EJ, Hilfiker-Kleiner D, Kamiya CA, Mazzarotto F, Cook SA, Halder I, Prasad SK, Pisarcik J, Hanley-Yanez K, Alharethi R, Damp J, Hsich E, Elkayam U, Sheppard R, Kealey A, Alexis J, Ramani G, Safirstein J, Boehmer J, Pauly DF, Wittstein IS, Thohan V, Zucker MJ, Liu P, Gorcsan J 3rd, McNamara DM, Seidman CE, Seidman JG, Arany Z, IMAC-2 and IPAC Investigators (2016) Shared genetic predisposition in peripartum and dilated cardiomyopathies. N Engl J Med 21(374):233–241
34. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C, Smith SC Jr, Jacobs AK, Adams CD, Antman EM, Anderson JL, Hunt SA, Halperin JL, Nishimura R, Ornato JP, Page RL, Riegel B, Blanc JJ, Budaj A, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL, American College of Cardiology/American Heart Association Task Force, European Society of Cardiology Committee for Practice Guidelines, European Heart Rhythm Association, Heart Rhythm Society (2006) ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation 114:e385–e484
35. Echt DS, Liebson PR, Mitchell LB, Peters RW, Obias-Manno D, Barker AH, Arensberg D, Baker A, Friedman L, Greene HL et al (1991) Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. N Engl J Med 324:781–788
36. Lemery R, Brugada P, Bella PD, Dugernier T, van den Dool A, Wellens HJ (1989) Nonischemic ventricular tachycardia. Clinical course and long-term follow-up in patients without clinically overt heart disease. Circulation 79:990–999
37. Brodsky M, Doria R, Allen B, Sato D, Thomas G, Sada M (1992) New-onset ventricular tachycardia during pregnancy. Am Heart J 123(4 Pt 1):933–941
38. Cleary-Goldman J, Salva CR, Infeld JI, Robinson JN (2003) Verapamil-sensitive idiopathic left ventricular tachycardia in pregnancy. J Matern Fetal Neonatal Med 14:132–135
39. Dalvi BV, Chaudhuri A, Kulkarni HL, Kale PA (1992) Therapeutic guidelines for congenital complete heart block presenting in pregnancy. Obstet Gynecol 79(5 (Pt 2)):802–804
40. Hidaka N, Chiba Y, Fukushima K, Wake N (2011) Pregnant women with complete atrioventricular block: perinatal risks and review of management. Pacing Clin Electrophysiol 34:1161–1176
41. Rashba EJ, Zareba W, Moss AJ, Hall WJ, Robinson J, Locati EH, Schwartz PJ, Andrews M (1998) Influence of pregnancy on the risk for cardiac events in patients with hereditary long QT syndrome. LQTS investigators. Circulation 97:451–456
42. Shimizu W, Tanabe Y, Aiba T, Inagaki M, Kurita T, Suyama K, Nagaya N, Taguchi A, Aihara N, Sunagawa K, Nakamura K, Ohe T, Towbin JA, Priori SG, Kamakura S (2002) Differential effects of beta-blockade on dispersion of repolarization in the absence and presence of sympathetic stimulation between the LQT1 and LQT2 forms of congenital long QT syndrome. J Am Coll Cardiol 39:1984–1991
43. Chockalingam P, Crotti L, Girardengo G, Johnson JN, Harris KM, van der Heijden JF, Hauer RN, Beckmann BM, Spazzolini C, Rordorf R, Rydberg A, Clur SA, Fischer M, van den Heuvel F, Kääb S, Blom NA, Ackerman MJ, Schwartz PJ, Wilde AA (2012) Not all beta-blockers are

equal in the management of long QT syndrome types 1 and 2: higher recurrence of events under metoprolol. J Am Coll Cardiol 60:2092–2099
44. Abu-Zeitone A, Peterson DR, Polonsky B, McNitt S, Moss AJ (2014) Efficacy of different beta-blockers in the treatment of long QT syndrome. J Am Coll Cardiol 64:1352–1358
45. Food and Drug Administration, HHS (2014) Content and format of labeling for human prescription drug and biological products; requirements for pregnancy and lactation labeling. Final rule. Fed Regist 79:72063–72103
46. Joglar JA, Page RL (2014) Management of arrhythmia syndromes during pregnancy. Curr Opin Cardiol 29:36–44
47. Cox JL, Gardner MJ (1993) Treatment of cardiac arrhythmias during pregnancy. Prog Cardiovasc Dis 36:137–178
48. Donofrio MT, Moon-Grady AJ, Hornberger LK, Copel JA, Sklansky MS, Abuhamad A, Cuneo BF, Huhta JC, Jonas RA, Krishnan A, Lacey S, Lee W, Michelfelder EC Sr, Rempel GR, Silverman NH, Spray TL, Strasburger JF, Tworetzky W, Rychik J, American Heart Association Adults With Congenital Heart Disease Joint Committee of the Council on Cardiovascular Disease in the Young and Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and Council on Cardiovascular and Stroke Nursing (2014) Diagnosis and treatment of fetal cardiac disease: a scientific statement from the American Heart Association. Circulation 129:2183–2242
49. Horigome H, Takahashi MI, Asaka M, Shigemitsu S, Kandori A, Tsukada K (2000) Magnetocardiographic determination of the developmental changes in PQ, QRS and QT intervals in the foetus. Acta Paediatr 89:64–67
50. Easterling TR, Brateng D, Schmucker B, Brown Z, Millard SP (1999) Prevention of preeclampsia: a randomized trial of atenolol in hyperdynamic patients before onset of hypertension. Obstet Gynecol 93:725–733
51. Frishman WH, Chesner M (1988) Beta-adrenergic blockers in pregnancy. Am Heart J 115:147–152
52. Lydakis C, Lip GY, Beevers M, Beevers DG (1999) Atenolol and fetal growth in pregnancies complicated by hypertension. Am J Hypertens 12:541–547
53. Lip GY, Beevers M, Churchill D, Shaffer LM, Beevers DG (1997) Effect of atenolol on birth weight. Am J Cardiol 79:1436–1438
54. Strasburger JF, Cuneo BF, Michon MM, Gotteiner NL, Deal BJ, McGregor SN, Oudijk MA, Meijboom EJ, Feinkind L, Hussey M, Parilla BV (2004) Amiodarone therapy for drug-refractory fetal tachycardia. Circulation 109:375–379
55. Lomenick JP, Jackson WA, Backeljauw PF (2004) Amiodarone-induced neonatal hypothyroidism: a unique form of transient early-onset hypothyroidism. J Perinatol 24:397–399
56. Wang YC, Chen CH, Su HY, Yu MH (2006) The impact of maternal cardioversion on fetal haemodynamics. Eur J Obstet Gynecol Reprod Biol 126:268–269
57. Barnes EJ, Eben F, Patterson D (2002) Direct current cardioversion during pregnancy should be performed with facilities available for fetal monitoring and emergency caesarean section. BJOG 109:1406–1407
58. Patel SJ, Reede DL, Katz DS, Subramaniam R, Amorosa JK (2007) Imaging the pregnant patient for nonobstetric conditions: algorithms and radiation dose considerations. Radiographics 27:1705–1722
59. Best PJ, Skelding KA, Mehran R, Chieffo A, Kunadian V, Madan M, Mikhail GW, Mauri F, Takahashi S, Honye J, Hernández-Antolín R, Weiner BH, Society for Cardiovascular Angiography & Interventions' Women in Innovations (WIN) group (2011) SCAI consensus document on occupational radiation exposure to the pregnant cardiologist and technical personnel. Catheter Cardiovasc Interv 77:232–241
60. Tuzcu V, Kilinc OU (2012) Implantable cardioverter defibrillator implantation without using fluoroscopy in a pregnant patient. Pacing Clin Electrophysiol 35:e265–e266
61. Natale A, Davidson T, Geiger MJ, Newby K (1997) Implantable cardioverter-defibrillators and pregnancy: a safe combination? Circulation 96:2808–2812

62. Miyoshi T, Kamiya CA, Katsuragi S, Ueda H, Kobayashi Y, Horiuchi C, Yamanaka K, Neki R, Yoshimatsu J, Ikeda T, Yamada Y, Okamura H, Noda T, Shimizu W (2013) Safety and efficacy of implantable cardioverter-defibrillator during pregnancy and after delivery. Circ J 77:1166–1170
63. Frett JD (2015) Wearable cardioverter defibrillator for peripartum cardiomyopathy patients. Eur J Heart Fail 17:234
64. Reuschel E, Baessler A, Stöllberger C, Finsterer J, Maier L, Fischer M, Poschenrieder F, Heissenhuber F, Kurzidim K, Schepp CP, Badelt G, Seelbach-Göbel B (2016) Interdisciplinary management of left ventricular hypertrabeculation/noncompaction during pregnancy with a wearable defibrillator. Int J Cardiol 15(223):154–158

Fetal Cardiac Disease

17

Keiko Ueda

Abstract

The optimal management of pregnancies involving fetal congenital anomalies is important because the events of perinatal period are strongly associated with perioperative mortality and long-term outcomes. Congenital heart disease (CHD) is one of the most prominent birth defects; however, few reports on obstetrical issues in pregnancy with fetal CHD have been published. In this chapter, we review antenatal and intrapartum management for fetuses with CHD focusing particularly on intrapartum electrical fetal heart rate (FHR) monitoring in CHD patients.

FHR monitoring has been widely used for antenatal and intrapartum management. Our previous study demonstrated that fetuses with structural heart anomalies tended to show variant heart rate patterns such as severe variable deceleration, recurrent late deceleration, prolonged deceleration, and loss of baseline variability. Single ventricle, isomerism, and tetralogy of Fallot frequently showed variant FHR patterns. Conversely, umbilical artery pH results showed that most CHD fetuses with variant FHR patterns did not have accompanying acidosis, even in cases of emergency Caesarean section (C-section). These data suggested that special consideration is needed when translating the findings of aberrant FHR patterns in fetuses with CHD. Although FHR monitoring is among the most validated tools to detect nonreassuring fetal status, additional strategies should be discussed in the future due to the difficulty of monitoring fetal well-being in CHD patients.

Keywords

Congenital heart disease · Fetal heart rate monitoring · Variant fetal heart rate pattern

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17.1 Introduction

Congenital heart disease (CHD) is one of the most frequently reported fetal anomalies, seen in 1 in 100 live newborns. One-third of CHD patients present severe forms associated with early infantile mortality. Despite the difficulty of accurate fetal diagnoses, remarkable advances of echocardiographic imaging in the last decade have contributed to increased early detection of structural heart defects. Intrauterine diagnosis and antenatal management are critical for determining the optimal interventions after birth, including catheter intervention (balloon atrial septostomy (BAS), etc.) or artificial respiratory or circulation support (extracorporeal membrane oxygenation (ECMO), etc.). Fetal and neonatal hemodynamics, as well as fetal well-being, are taken into consideration when making a birth plan. A team of fetal-maternal medicine specialists and cardiologists is required for understanding the whole picture of early-life treatment for patients diagnosed with CHD.

With these efforts in medical care, neonatal and infantile mortality due to CHD has dramatically decreased in recent years. However, it remains important to discuss the accompanying perinatal risks and their ideal management during pregnancy for CHD patients.

In this chapter, we discuss the optimal antenatal and intrapartum monitoring of fetal well-being using ultrasound evaluation or electronic fetal heart rate (FHR) monitoring.

17.2 Fetal Diagnosis: Screening and Detailed Diagnosis of Fetal Heart Disease

The primary goal of fetal management in CHD patients is to improve the perinatal outcome and long-term prognosis. To achieve this goal, the management of fetal cardiac disease should start from antenatal diagnoses. Pregnant women are highly recommended to join an antenatal screening program using fetal echocardiography. When abnormality is detected in fetal hearts by screening, fetal and pediatric cardiologists can perform more detailed assessments to propose ideal postnatal treatment plans according to the risk stratification.

The effectiveness of prenatal diagnosis of major CHD has been thoroughly discussed in previous published articles [1–9]. The postnatal courses of some patients become complicated if they are born without fetal diagnosis and outside the appropriate institutions, because some critical types of CHD develop into cardiac compromise shortly after birth. Several articles have suggested that fetal diagnosis and ideal postnatal care minimize the risk of death from cardiovascular deterioration prior to attempted neonatal cardiac surgery relative to cases diagnosed postnatally [1, 2]. For example, hypoplastic left heart syndrome (HLHS) is one of the most severe forms of patent ductus arteriosus (PDA)-dependent cardiac defects and requires both detailed examination of postnatal hemodynamics and specialized knowledge of perinatal management, which includes not only pediatric surgery but also pharmaceutical support to prevent cardiovascular compromise or respiratory

failure [2, 3]. A certain type of transposition of the great arteries (TGA) or intact ventricular septum with a restrictive foramen ovale (FO), ductus arteriosus (DA) constriction, or pulmonary hypertension may develop severe hypoxemia and become lethal immediately after birth. Careful preparation for BAS or neonatal cardiac surgery is essential for postnatal management [5, 6]. Prenatal diagnosis in fetuses with tetralogy of Fallot (TOF), coarctation of the aorta (COA), or truncus arteriosus similarly improves their neonatal outcomes [7–9].

However, several issues are debated regarding the ethical aspects of early diagnoses. A high rate of artificial abortion has been reported after antenatal diagnoses of critical CHD [10]. Fetuses with CHD are often identified with coexisting deformities or genetic syndromes associated with undesirable prognoses. A multidisciplinary approach is required for the treatment of CHD infants. Experts from all fields of fetal-maternal medicine should work together with other specialists in genetics or ethics depending on the problem [11]. Families should be carefully informed about the current conditions of their babies and long-term prognoses to provide consent for birth plans and postnatal treatment. Because of the logistical and economic challenges for parents of such babies, social or public aid may play a pivotal role in their decisions. Moreover, the patients-caregiver relationship or family support could influence neonatal and infantile treatment decisions and the future growth and development of patients affected by CHD.

17.3 Antenatal Management: Obstetrical Management and Cardiologist Perspectives

Intrapartum management for pregnancies with fetal congenital heart anomalies is not clearly described in the obstetrical textbooks or literature. Thus, it is often unclear how to evaluate the well-being of patients with CHD or what are the best methods and timing of care delivery.

An accurate understanding of both cardiovascular morphology and hemodynamics is critical to determine the best strategy for perinatal management. Fetal cardiac function is usually evaluated by ultrasound methods such as ejection fraction, cardiac output, strain or strain ratio, E/A ratio, and isovolumic reaction time (IRT) [12]. Recent technological advances in echocardiography, including spatio-temporal image correlation (STIC) and tissue Doppler imaging (TDI), may contribute to the understanding of both detailed structural defects and cardiac function. Other biomarkers for the early detection of fetal heart failure have recently been investigated [13]. The combination of these parameters enable detection of the early signs of deterioration in fetal cardiac function, and once fetal heart failure progresses, hydrops or arrhythmia can sometimes easily seen by ultrasound examination.

When deciding the timing of delivery, dynamic changes of hemodynamics from fetal to postnatal circulation should be discussed regarding the balance of benefit between intrauterine life and postnatal treatment. In the extreme example of Ebstein's anomaly, a circular shunt is often observed based on functional pulmonary atresia with absent forward flow. Circular blood flow occurs left to right across the

patent ductus arteriosus, retrograde through the pulmonary artery and Ebstein valve, across the patent foramen ovale, and out the aorta. Although the quantitative estimation of postnatal hemodynamics is difficult, a detailed examination of fetal circulation provides some insight of CHD severity.

Some general obstetrical and gynecological issues for pregnancies with CHD fetuses have been reported in relatively few papers [14, 15]. Pregnancies affected by CHD fetuses are associated with several adverse obstetric and neonatal outcomes. One population-based cohort in Sweden displayed increased risks for preeclampsia, preterm delivery, small size for gestational ages, and meconium aspiration [15]. Another study showed that fetuses with CHD have a threefold greater risk of developing intrauterine growth restriction [14]. The presence of other abnormalities hugely impacts prognoses and could be important for perinatal management. All of these fetal conditions are important when assessing pregnancy variables, as are obstetrical assessments such as uterine contractions and cervical length. Essential examinations for pregnant women should be performed, including fetal ultrasounds (biophysical profile score (BPS), amniotic fluid index (AFI), and fetal growth) or electronic FHR monitoring, but special additional knowledge of pregnancies with fetal CHD is required when discussing their management. All information should be integrated and discussed comprehensively when determining the optional timing and mode of delivery.

In the next section, we explore the obstetrical aspects of fetal heart disease, particularly FHR monitoring patterns in fetuses with congenital heart disease.

17.4 Intrapartum Management

17.4.1 Fetal Heart Rate Monitoring in Fetuses with CHD

Electronic FHR monitoring is one of the most recognized fetal management tools. It is often conducted at each hospital visit during pregnancy and repeatedly applied because of its easiness and convenience. FHR is continuously monitored and recorded until babies are born by spontaneous delivery or Caesarian section. The interpretation of fetal heart rate pattern is well established. Nonreassuring FHR patterns represent fetal distress and have huge clinical importance as a measurement of fetal oxygenation and acid-base status. This measurement may inform the next step of fetal-maternal management, whether action or waiting for spontaneous recovery.

FHR patterns are produced by the autonomic nervous system, composed of the sympathetic and parasympathetic nerves connecting the heart to the brain. This physiological understanding suggests that the structural abnormality of those cycles might influence the patterns of FHR. Several reports have addressed the unexpected aberrant patterns generated by congenital anomalies in FHR monitoring, especially the strong association between aberrant FHR patterns and anomalies of the central nervous system [16–18]. Conversely, relatively few articles examine the FHR patterns of congenital disease. Gertie et al., for example, analyzed several CHD patients

for FHR in association with congenital anomalies [16]. Here, we introduce the results of our research and discuss FHR monitoring for congenital cardiovascular defects.

17.4.1.1 Research Question 1: Is There Any Difference in the Prevalence of Caesarean Sections due to Variant FHR Patterns in CHD?

FHR patterns of fetuses with congenital heart disease (CHD) were analyzed [19]. We retrospectively examined the FHR records of 116 CHD cases delivered from 2000 to 2007 at the National Cardiovascular Center, Osaka, Japan. Corresponding to each study subject, four consecutive controls matched for gestational age and birth weight were selected. All CHD cases were diagnosed in utero using ultrasound and classified into 12 categories: heart isomerism, univentricular heart (UVH), TOF, transposition of the great arteries, double outlet of the right ventricle, HLHS, common arteriovenous canal, ventricular septal defect, coarctation or interruption of the arch (COA/IAA), aortic stenosis, pulmonary stenosis or atresia (PS/PA), and an "other" category consisting of fewer than 5 cases. Demographic and historical characteristics were compared between the groups.

Table 17.1 shows the background data of each group. When controlling for birth weight and gestational age, an Apgar score of less than 7 was significantly more prevalent in infants with CHD than in the controls at both 1 (17.2% vs. 6.0%, $p < 0.05$) and 5 (9.5% vs 1.5%, $p < 0.05$) min after birth. The summary of the mode of delivery for CHD patients and controls is also shown in Table 17.1. Patients affected by CHD were more likely to be delivered by emergency Caesarean section, but this difference was not statistically significant. The incidence of emergency

Table 17.1 Population characteristics

Characteristics	Study subjects ($n = 116$)	Control patients ($n = 464$)	P value
Birth weight (g)	2729 ± 553	2754 ± 531	NS
Gestational age (w)	38 + 2	38 + 2	NS
Apgar score			
<7 (1 min)	20 (17.2%)	28 (6.0%)	<0.05
<7 (5 min)	11 (9.5%)	5 (1.0%)	<0.05
Sex			
Male	63 (54.3%)	245 (52.8%)	NS
Female	53 (45.7%)	219 (47.2%)	NS
Delivery			
Induction	55 (47.4%)	204 (44.0%)	NS
Operative	18 (15.5%)	45 (9.7%)	NS
Emergency CS	29 (25.0%)	84 (18.1%)	NS
Due to variant FHR	15 (12.9%)	15(3.2%)	<0.05
Due to arrest of delivery	14 (12.1%)	69 (14.9%)	NS

Ueda K, et.al., Am J Obstet Gynecol. 2009 Jul;201(1):64.e1-6
NS not significant, *CS* cesarean section

Table 17.2 Incidence of FHR deceleration and minimal baseline variability in patients with congenital heart disease

Characteristics	Study subjects (n = 116)	Control patients (n = 464)	P value
Severe variable	35 (30.2%)	40 (8.6%)	<0.05
Prolonged	11 (9.5%)	15 (3.2%)	<0.05
Recurrent late	4 (3.4%)	23 (5.0%)	NS
Loss/decreased variability	4 (3.4%)	4 (0.9%)	NS
None	62 (53.4%)	384 (82.3%)	<0.05

Ueda K, et.al., Am J Obstet Gynecol. 2009 Jul;201(1):64.e1-6
NS not significant

Caesarean section due to variant FHR patterns was significantly higher in CHD patients (12.9% vs 3.2%, $p < 0.01$). However, the frequency of emergency Caesarean section due to other reasons, such as arrest of delivery or induction delivery, did not differ between groups.

Table 17.2 shows the incidence of each aberrant FHR pattern in patients with CHD. All signs of FHR were assessed according to the National Institutes of Child Health and Human Development guideline [20]. Aberrant patterns of FHR were observed in 46.6% of patients with CHD, which was significantly higher than the incidence of controls (17.7%, $p < 0.01$). Severe variable deceleration was found more frequently during the delivery of patients affected by CHD compared to the controls (30.2% vs 8.6%, $p < 0.01$), as was prolonged deceleration (9.5% vs 3.2%, $p < 0.01$). Fewer cases were observed with recurrent late deceleration and lost or decreased baseline variability, and no significant differences were found between the two groups.

Our findings are consistent with those of previous population cohort studies [15, 21] showing high rates of emergency Caesarean sections or fetal distress in CHD patients. Other articles have reported that a high prevalence of Caesarean sections is mainly seen in multiparous pregnancies [22]. The lack of information about null and multiparous pregnancies in our data could have limited our observations. Additionally, as is common in retrospective analysis, the indication of intervention was not perfectly manipulated. This limitation occurred due to the physicians' intolerance when looking at severe structural defects at risk of unfavorable prognoses or variant patterns of FHR in fetuses with CHD.

Although the generalizability of small studies is debatable, we believe an important clinical implication can be drawn from our results: fetuses diagnosed with CHD are more likely to show intrapartum aberrant FHR patterns, which often indicate an emergency Caesarean section.

17.4.1.2 Research Question 2: What Subtypes of CHD Most Likely Show Variant FHR Patterns?

Because congenital malformations constitute a heterogeneous group of structural lesions, our next research question considered what types of heart defect tend to be associated with aberrant FHR patterns.

Table 17.3 Incidence of variant FHR patterns in subjects of CHD

Subjects of CHD (*n*)	Variant FHR	Severe VD	Prolonged D	Recurrent LD	Minimum variability	Normal FHR
Isomerism (*n* = 13)	6 (46.2%)[a]	1	3	0	2	7
UVH (*n* = 8)	6 (75.0%)[a]	3	3	0	0	2
TOF (*n* = 12)	10 (83.3%)[a]	7	1	1	1	2
DORV (*n* = 7)	1 (14.3%)	1	0	0	0	6
VSD (*n* = 8)	3 (37.5%)	3	0	0	0	5
HLHS (*n* = 7)	2 (28.6%)	1	0	1	0	5
TGA (*n* = 7)	2 (28.6%)	2	0	0	0	5
AS (*n* = 7)	4 (57.1%)[a]	4	0	0	0	3
CAVC (*n* = 7)	2 (28.6%)	1	0	1	0	5
PS/PA (*n* = 5)	2 (40.0%)	1	1	0	0	3
CoA/IAA (*n* = 13)	6 (46.2%)[a]	4	0	1	1	7
Others (*n* = 22)[b]	10 (45.5%)	7	3	0	0	12
Total (*n* = 116)	54 (46.6%)	35	11	4	4	62

Ueda K, et.al., Am J Obstet Gynecol. 2009 Jul;201(1):64.e1-6

[a]Incidence of variant FHR patterns of this category was significantly higher than that of study subjects ($p < 0.05$)

[b]Others included Ebstein's anomaly ($n = 4$), truncus of the arteriosus ($n = 2$), heart tumor ($n = 4$), and patent ductus arteriosus ($n = 2$)

UVH: univentricular heart; *TOF*: tetralogy of Fellot; *DORV*: double-outlet right ventricle; *VSD*: ventricular septal defect; *HLHS*: hypoplastic left heart syndrome; *TGA*: transposition of the great arteries; *AS*: aortic stenosis; *CAVC*: common atrio-ventricular canal; *PS/PA*: pulmonary stenosis/pulmonary atresia; *COA/IAA*: coactation of aorta/interrupted aortic arch

Table 17.3 presents the analysis of deceleration patterns of FHR fetuses according to the subtype of fetal diagnosis. Fetuses with TOF (83.3%), UVH (75%), aortic stenosis (57.1%), isomerism (46.2%), and COA/IAA (57.1%) showed statistically higher incidences of variant FHR patterns. Ebstein's anomalies corresponded to higher occurrence of variant FHR patterns, but few cases were included ($n = 4$). After excluding 44 fetuses associated with IUGR, chromosomal abnormalities, or other major structural anomalies that might have confounded the interpretation of FHR patterns, aberrant patterns were still frequently detected in the FHR of study subjects compared to the controls (38.8% vs. 17.7%, $p < 0.05$), in particular for cases with TOF or UVH. Severe variable deceleration and prolonged deceleration were the most visible patterns among fetuses with CHD.

Although the samples were limited, the data may imply that structural features originating in the early stages of heart development and involving a larger lesion of deformities tend to present aberrant patterns. Right or left heart isomerism is a positioning disarrangement usually diagnosed with heterotaxy or spleen abnormality. The normal arrangement of the viscera is disrupted and commonly associated with

single anatomies of the ventricle. Single ventricle is a structural abnormality in which only one ventricle occurs in the heart, which significantly impairs normal blood flow. Compared to cases of CHD with a four-chamber structure in situs solitus, single ventricle contains more complexity in anatomy and embryology. The dynamic alterations of morphology and physiology may confuse autonomic nervous system control because the pathways of those nerves could be affected by the deformity.

Another explanation is required for the development of aberrant FHR patterns with TOF, PS/PA, and COA/IAA. All of these deformities present pressure overload on the ventricles. After eliminating IUGR or other major anomalies, COA/IAA did not have a high incidence of apparent FHR; therefore, CHD involving right ventricle pressure overload could impact FHR patterns. Although the number of cases was small, other heart conditions involving right ventricle pressure load, such as right heart tumor ($n = 2$, 100%, variant FHR) and hypertrophy of the right ventricle of unknown cause ($n = 1$, 100%, variant FHR), were also observed in this study.

Cases of CHD with normal four-chamber anatomy, including ventricular septal defect (VSD), common arteriovenous truncus (CAVD), double outlet of the right ventricle (DORV), and conotruncal abnormalities such as transpositions of great arteries (TGA) [22], seem to support an intact electrical conduction system. However, these cases display a variety of structural defects, and severity differs widely among them. Careful interpretation of the results and a larger sample size are required. Additionally, the ambiguity of fetal diagnosis should be considered when translating the study findings to the practical world, because TGA is among the most intricate types of CHD for fetal echocardiographic examination.

17.4.2 Umbilical Arterial pH

Umbilical blood testing has been used for the retrospective evaluation of intrauterine fetal oxygenation. Umbilical arterial pH can be easily obtained after delivery without any invasion of the mother or fetus. Low values of pH indicate fetal acidosis in utero, and a pH < 7.2 is usually considered abnormal. Variant FHR patterns are well correlated with fetal acidotic status during delivery as reflected by umbilical

Table 17.4 Comparison of umbilical arterial pH between the groups

pH	Study subjects ($n = 116$)	Control patients ($n = 464$)	*P* value
Average	7.290 ± 0.097	7.304 ± 0.076	NS
<7.0	2 (1.7%)	2 (0.9%)	NS
7.0–7.1	2 (3.4%)	7 (1.9%)	NS
7.1–7.2	8 (10.3%)	26 (7.5%)	NS
>7.2[a]	104	429	NS

Ueda K, et.al., Am J Obstet Gynecol. 2009 Jul;201(1):64.e1-6

NS not significant

[a]7.2 > pH: tetralogy of Fallot 3, isomerism 3, ventricular septal defect 2, univentricular heart 2, common atrio-ventricular canal 1, hypoplastic aorta 1

Table 17.5 Comparison of umbilical arterial pH in emergency C-section cases between the groups

pH	Study subjects ($n = 15$)	Control patients ($n = 15$)	P value
Average	7.307 ± 0.041	7.249 ± 0.134	NS
<7.0	0	1 (6.7%)	NS
7.0–7.1	0	1 (13.3%)	NS
7.1–7.2	0	1 (20.0%)	NS
>7.2	15	12	NS

Ueda K, et.al., Am J Obstet Gynecol. 2009 Jul;201(1):64.e1-6
NS not significant

arterial pH. Therefore, variant FHR patterns and acidotic findings from umbilical arterial pH should be associated.

Table 17.4 shows that umbilical arterial pH values were similar in both groups (study subjects vs controls, 7.290 ± 0.098 vs 7.304 ± 0.076). These data suggest that no significant differences occurred between the two groups in fetal acidotic status. Interestingly, this pattern was also observed in the subgroup delivered by emergency Caesarian section due to variant FHR (7.307 ± 0.041 vs 7.249 ± 0.134, respectively: $p > 0.05$). Two cases with umbilical arterial pH < 7.2 were observed among the controls, but no cases were observed among patients with CHD (Table 17.5).

Our data suggest a discrepancy in the clinical interpretation of findings from FHR monitoring and umbilical arterial pH in patients with CHD. It is puzzling that variant patterns of FHR in CHD patients cannot be translated in the same way as for patients without CHD. One possible interpretation may involve the mechanisms of formulating FHR patterns. Fetal autonomic activity has been established as a reliable marker of central nervous system function and could be reflected in the control of fetal heart rate. Therefore, an abnormality of the brain, heart, and nerves that connects two organs may be associated with variant FHR patterns. Some types of CHD are likely to accompany variant FHR, but the correlation between FHR patterns and real fetal acidosis could be confounded or even exaggerated by the unique features of the autonomic conduction system. This hypothesis is supported by the observations of Siddiqui et al., who found that autonomic development in fetuses with CHD began to detectably deviate from the normal trajectory of autonomic nervous system regulation within 19 weeks of gestation [23].

Further investigations are needed to determine the relationship between aberrant patterns in CHD patients and the mechanism of formulating FHR patterns.

17.4.3 Other Tools for Evaluating Fetal Well-Being for CHD

FHR monitoring is a well-validated tool for the evaluation of fetal well-being. However, this method is limited when examining fetuses with fetal acidosis and structural heart defects. Aside from FHR monitoring, fetal echocardiography, and umbilical arterial pH values, relatively few tools exist for the fetal diagnosis of fetal

distress. Before delivery onset, the risks of progressing acidosis can be evaluated by a low BPS score, blood flow, or resistance in fetal brain vessels or umbilical vessels. Fetal scalp blood sampling of pH or lactate can examine fetal acidosis directly, but this invasive procedure is seldom performed. The use of fetal scalp blood sampling data for intrapartum management in an emergency situation is unrealistic.

Several other studies have examined fetal well-being and CHD [22, 24]. A fetal oximeter can measure fatal oxygenation directly during the intrapartum period. This new device is expected to determine fetal distress with high sensitivity and specificity, thereby reducing Caesarian section rates. Considering the present evidence from the Cochrane review, which compiled negative data from several systematic studies (including six comparing fetal pulse oximetry and FHR vs DHR alone), it remains difficult to conclude that the fetal oximeter provides a strong alternative to FHR monitoring [24]. A better method or improved device for pulse oximetry is necessary to enhance the overall evaluation of fetal well-being during labor. Another possibility is the evaluation of the ST segment in fetal electrocardiography. Gay et al. compared the frequencies of different ST events between fetuses with and without CHD. Their results showed that CHD does not modify the frequencies of ST events [22]. Fetal electrocardiography (STAN) was developed to avoid unnecessary Caesarean sections due to suspected fetal acidosis. The mechanism of STAN is related to heart muscle oxygenation and the biphasic ST segment, and T/QRS ratios represent fetal hypoxic episodes. The clinical translation of this study data is challenging, as the authors did not provide the data of their FHR monitoring, but the results could be useful for further investigation of the relationship between aberrant HFR patterns and patients with CHD.

17.5 Conclusion and Further Research Questions

Some observations introduced in this chapter still require further examination. However, in conclusion, these findings generate relevant clinical implications and suggest new research questions for both obstetricians and fetal and pediatric cardiologists.

A better understanding of fetal physiology and innovative thinking could help solve several remaining problems in pregnancies involving CHD fetuses. Although several operational devices or technical innovations could be applied to improve the long-term mortality and morbidity of CHD infants, these technologies would still not fulfil physician and patient demands. Furthermore, fetal interventions have been widely discussed to support term pregnancies or improve fetal circulation status in several types of CHD. To generate new technological advancements, more detailed investigation of the basics of fetal life is important. A more sophisticated collaborative approach between a variety of experts in the field should be established to address this challenge [25].

True innovation will arise from a careful analysis of present technology, and physicians should identify its current limitations. Many opportunities remain in this field for both daily practice and research.

References

1. Holland BJ, Myers JA, Woods CR Jr (2015) Prenatal diagnosis of critical congenital heart disease reduces risk of death from cardiovascular compromise prior to planned neonatal cardiac surgery: a meta-analysis. Ultrasound Obstet Gynecol 45(6):631–638
2. Levey A, Glickstein JS, Kleinman CS et al (2010) The impact of prenatal diagnosis of complex congenital heart disease on neonatal outcomes. Pediatr Cardiol 31:587–597
3. Satomi G, Yasukouchi S, Shimizu T et al (1999) Has fetal echocardiography improved the prognosis of congenital heart disease? Comparison of patients with hypoplastic left heart syndrome with and without prenatal diagnosis. Pediatr Int 41:726–732
4. Tworetzky W, McElhinney DB, Reddy VM et al (2001) Improved surgical outcome after fetal diagnosis of hypoplastic left heart syndrome. Circulation 103:1269–1273
5. Coltri A, Burtera G et al (1999) Detection of transposition of the great arteries in fetuses reduces neonatal morbidity and mortality. Circulation 99:916–918
6. Maeno YV, Kamenir SA, Sinclare B et al (1999) Prenatal features of ductus arteriosus constriction and restrictive foramen ovale in d-transposition of the great arteries. Circulation 99:1209–1214
7. Duke C, Sharland GK, Jones AM et al (2001) Echocardiographic features and outcome of truncus arteriosus diagnosed during fetal life. Am J Cardiol 88:1379–1384
8. Franklin O, Burch M, Manning N et al (2002) Prenatal diagnosis of coarctation of the aorta improves survival and reduces morbidity. Heart 87:67–69
9. Pepas LP, Savis A, Jones A et al (2003) An echocardiographic study of tetralogy of Fallot in the fetus and infant. Heart 13:240–247
10. Smythe JF, Copel JA, Kleinman CS et al (1992) Outcome of prenatally detected cardiac malformation. Am J Cardiol 69:1471–1474
11. Sholler GF, Kasparian NA, Pye VE et al (2011) Fetal and post-natal diagnosis of major congenital heart disease: implications for medical and psychological care in the current era. J Paediatr Child Health 47(10):717–722
12. Crispi F, Gratacos E (2012) Fetal cardiac function: technical considerations and potential research and clinical applications. Fetal Diagn Ther 32:47–64
13. Luterek K1, Szymusik I, Bartkowiak R et al (2011) N-terminal pro-B-type natriuretic peptide: a potential marker of fetal heart failure in hemolytic disease. Neuro Endocrinol Lett 32(5):657–662
14. Wallenstein MB, Harper LM, Odibo AO et al (2012) Fetal congenital heart disease and intrauterine growth restriction: a retrospective cohort study. J Matern Fetal Neonatal Med 25(6):662–665
15. Cedergrena MI, Källénb BA (2006) Obstetric outcome of 6346 pregnancies with infants affected by congenital heart defects. Eur J Obstet Gynecol Reprod Biol 125(2):211–216
16. Gartie TJ, Linzey M, Freeman RK et al (1979) Fetal heart rate and fetal distress in fetuses with congenital anomalies. Obstet Gynecol 53:716–720
17. Biale Y, Brawer-Ostrovsky Y, Insler V (1985) Fetal heart rate tracing in fetuses with congenital malformation. J Reprod Med 30:43–47
18. Terao T, Kawasahima Y, Noto H et al (1984) Neurological control of fetal heart rate in 20 cases of anencephalic fetuses. Am J Obstet Gynecol 149:201–208
19. Ueda K, Ikeda T, Iwanaga N et al (2009) Intrapartum fetal heart rate monitoring in cases of congenital heart disease. Am J Obstet Gynecol 201(1):64.e1–64.e6
20. National Institutes of Child Health and Human Development Research Planning Workshop (1997) Electronic fetal heart rate monitoring: research guideline for interpretation. Am J Obstet Gynecol 177:1385–1390
21. Walsh CA et al (2014) Mode of delivery in pregnancies complicated by major fetal congenital heart disease: a retrospective cohort study. J Perinatol 34(12):901–905
22. Gay E, Bornallet G, Gaucherand P et al (2015) Intrapartum electrocardiogram alteration in fetuses with congenital heart disease: a case-control study. Eur J Obstet Gynecol Reprod Biol 194(8):111–114

23. Siddiqui S, Wilpers A, Myers M et al (2015) Autonomic regulation in fetuses with congenital heart disease. Early Hum Dev 91(3):195–198
24. East CE, Begg L, Colditz PB et al (2014) Fetal pulse oximetry for fetal assessment in labour. Cochrane Database Syst Rev 7(10)
25. Pavlovic M, Acharya G, Huhta JC (2008) Controversies of fetal cardiac intervention. Early Hum Dev 84(3):149–153

Fetal Arrhythmia

18

Takekazu Miyoshi

Abstract

Fetal arrhythmias present as an irregular cardiac rhythm and abnormal heart rate. Despite the theoretical advantage of fetoplacental circulation, rapid progression to hydrops is found in fetuses with tachyarrhythmia or bradyarrhythmia due to the limited heart rate reserve. Accurate diagnosis is essential for appropriate management of fetal arrhythmias, but this can be challenging since fetal electrocardiography is unavailable. Echocardiography plays a pivotal role in diagnosis and management of fetal arrhythmias. Most cases of fetal arrhythmia have a structurally normal heart with isolated premature contractions that often spontaneously resolve without medical treatment. There is a clear clinical consensus that maternal transplacental antiarrhythmic therapy for fetal tachyarrhythmia is effective. Complete atrioventricular block is irreversible. Dexamethasone and intravenous immunoglobulin have been used to prevent myocardial inflammation, but recent studies have not shown efficacy of these drugs for fetal bradyarrhythmias. Long QT syndrome manifests in several heart rate patterns and is associated with cardiac arrest and sudden death. Maternal intravenous magnesium is effective for ventricular tachycardia or torsades de pointes. This chapter reviews the different types of fetal arrhythmias and gives an overview of the current diagnostic techniques and treatment strategies.

Keywords

Bradycardia · Fetal arrhythmia · Fetal treatment · Prenatal diagnosis · Tachycardia

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18.1 Clinical Features

Arrhythmias present as an irregular cardiac rhythm, a slow or fast heart rate, or a combination of abnormal rhythm and rate. Fetal arrhythmias are observed in 1–2% of pregnancies at mid- to third trimester. Most cases evaluated for an irregular rhythm have isolated premature contractions with a structurally normal heart. Premature contractions usually spontaneously resolve without medical treatment [1]. In contrast, fetal tachyarrhythmias or bradyarrhythmias are rare but life-threatening, and medical treatment is usually necessary in utero and after birth. Most cases of congenital heart disease, even complex heart defect, can adapt in the fetal circulation. Despite the theoretical advantage of fetoplacental circulation, the circulatory reserve of an unborn child is negatively influenced by a variety of environmental and intrinsic factors, including the limited heart rate reserve. Because of the limited pump reserve of immature hearts, any significant change in heart rate leads to a decline in cardiac output, impaired cardiac filling, and venous congestion, the severity of which depends on arrhythmia characteristics and myocardial properties. Persistent tachyarrhythmias and bradyarrhythmias are among the more common cardiac causes of fetal hydrops, prematurity, and perinatal death [2, 3]. Hemodynamic evaluation using Doppler echocardiography permits elucidation of the electrophysiological mechanism and improves the accuracy of diagnosis. This method can also be used to understand fetal cardiac pathophysiology and to assess fetal conditions and monitor the effect of antiarrhythmic treatment. Abnormal venous Doppler sonography findings are common and severe in fetuses with tachy- or bradyarrhythmias and indicate elevation of central venous pressure. An increase in wall stress will result in cardiac remodeling and hypertrophy, which increases myocardial oxygen consumption and aggravates myocardial dysfunction. To overcome the reduction in ventricular compliance, end-diastolic filling pressure and hydrostatic central venous pressure increase to improve cardiac output [4]. As a result, rapid progression to hydrops occurs in fetuses with tachy- or bradyarrhythmias.

18.2 Diagnosis

18.2.1 Fetal Echocardiography

Accurate diagnosis is essential for management of fetal arrhythmias, and electrocardiography is the main diagnostic tool for arrhythmias in neonates, children, and adults. Noninvasive fetal electrocardiography is available at a few institutions but is too time-consuming to use in general clinical settings due to sensitivity and difficulty with analysis. Fetal echocardiography is usually used to assess fetal heart rate and rhythm, using 2D, M-mode, or pulsed Doppler imaging [5]. M-mode imaging is useful for simultaneous recording of atrial and ventricular systolic wall motions [6]. The relationship between atrial and ventricular contractions can be

shown, and heart rate can be measured. Simultaneous pulse wave Doppler evaluation of the superior vena cava and ascending aorta (SVC/aAo Doppler) is used to examine the sequence and time relationship of blood flow events secondary to atrial and ventricular contractions [7]. The beginning of the retrograde SVC wave reflects onset of atrial systole (A-wave), whereas onset of aortic forward flow marks the beginning of ventricular systole (V-wave). Diagnosis of fetal arrhythmias is made using the relationship between the A-wave and V-wave (Fig. 18.1). Each atrial event is followed by a ventricular event within a normal atrioventricular (AV) time interval, which confirms normal 1:1 AV conduction [8]. Fetal echocardiography is not an electrical assessment but a mechanical assessment. Hence, repolarization abnormalities such as long QT syndrome cannot be confirmed solely by echocardiography.

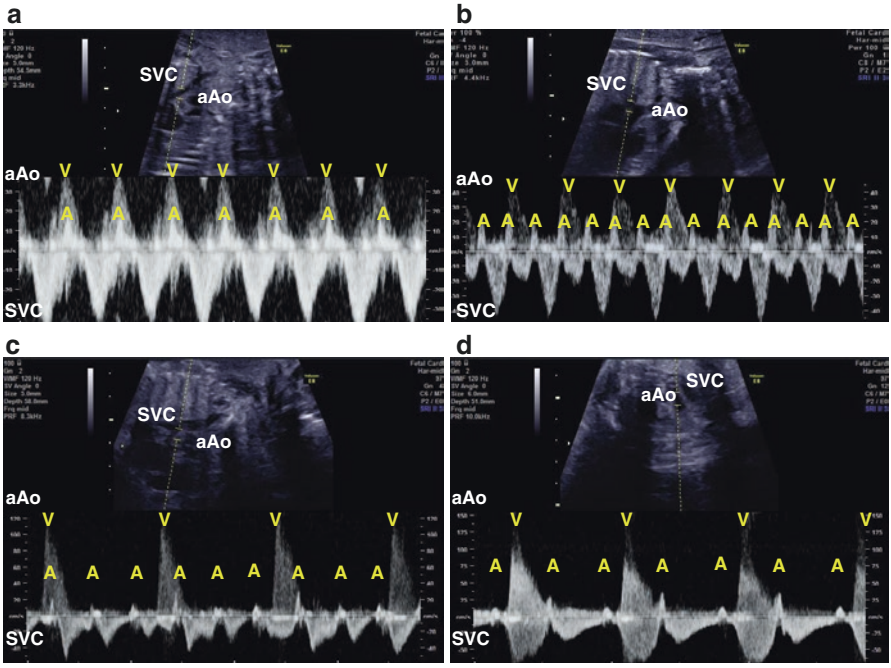

Fig. 18.1 Two-dimensional imaging showing a segment of the ascending aorta (aAo) adjacent to the superior vena cava (SVC) draining into the right atrium. Pulsed Doppler echocardiography shows aortic ejection waves (V-waves) recorded above the zero velocity line. Anterograde venous flow in the SVC in the opposite direction is shown below the line, and small venous retrograde waves (A-waves) caused by right atrial contraction are above the same line. (**a**) Fetal tachyarrhythmia with a short ventriculoatrial pattern, suggesting atrioventricular reentrant tachycardia. (**b**) Fetal tachyarrhythmias with 2:1 atrioventricular conduction, suggesting atrial flutter. (**c**) Fetal bradyarrhythmia with a regular normal atrial rhythm and rate but with the ventricles beating independently at a much slower rate, suggesting complete atrioventricular block. (**d**) Fetal bradyarrhythmia with 2:1 atrioventricular conduction, suggesting congenital second-degree atrioventricular block or functional atrioventricular block due to long QT syndrome

18.2.2 Cardiotocography

Cardiotocography traces fetal heart rate based on pulsed Doppler technology and is usually used for evaluating antepartum and intrapartum fetal well-being [9]. Similar to Holter electrocardiogram, cardiotocography can display uninterrupted segments of recorded time during normal rhythm or arrhythmias. In particular, cardiotocography plays an important role in management of fetal tachyarrhythmia, since it clearly shows the fetal heart rate baseline and frequency of fetal tachyarrhythmias, making it easy to evaluate the effects of fetal treatment. In addition, the clinical features of fetal ectopic atrial tachycardia (EAT) can be shown by cardiotocography. Fetal EAT has slow baseline changes that are referred to as a "warm-up and cool-down" phenomenon [10]. Onset and termination are sudden in most cases of reentrant supraventricular tachycardia (SVT) and atrial flutter (AFL) (Fig. 18.2a, b), whereas in EAT the shift of the pacemaker from the sinus node to the ectopic focus is more gradual. Thus, EAT shows a gradual increase after onset of tachycardia and a gradual decrease before termination of tachycardia (Fig. 18.2c). Another feature of fetal EAT on cardiotocography is short-term variability with acceleration during tachyarrhythmia [11].

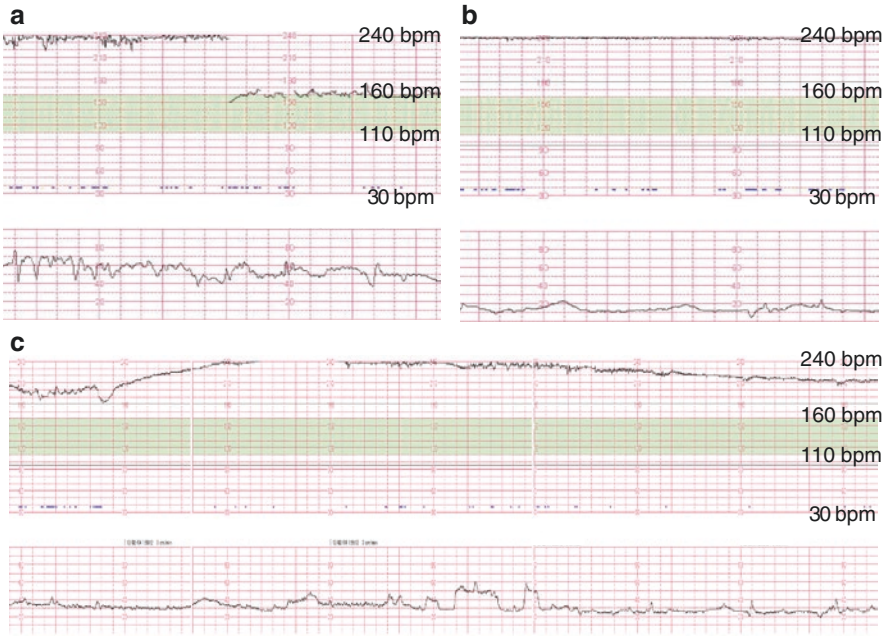

Fig. 18.2 Fetal cardiotocography showing (**a**) atrioventricular reentrant tachycardia with sudden termination of sinus rhythm, (**b**) atrial flutter with a flat baseline, (**c**) the fetal baseline accelerating gradually from 200 to over 240 bpm and decelerating gradually from 240 to 200 bpm, indicating a "warm-up and cool-down" phenomenon of ectopic atrial tachycardia

18.2.3 Fetal Magnetocardiography

Fetal magnetocardiography (fMCG) is used to assess electromagnetic characteristics of fetal cardiac conduction. Measurement must be performed in a shielded room that excludes magnetic interference from environmental sources [12]. Because of the requirement for specialized equipment and expertise, fMCG is currently performed in only a few institutions worldwide. fMCG captures the P-wave, PR interval, QRS interval, ST-T waves, QT interval, and RR interval in most fetuses at >24 weeks of gestation (Fig. 18.3a) [13, 14] and may be especially useful for analyzing complex rhythm and rate patterns such as irregular, multiple, or transient arrhythmias and for providing a more accurate differential diagnosis of tachy- and bradyarrhythmia. No other current method can detect repolarization abnormalities such as T-wave alternans [15]. Although fMCG currently has limited availability, use of this technique is reasonable for assessment of cardiac conduction and rhythm in fetuses with a known or suspected disease of the conduction system.

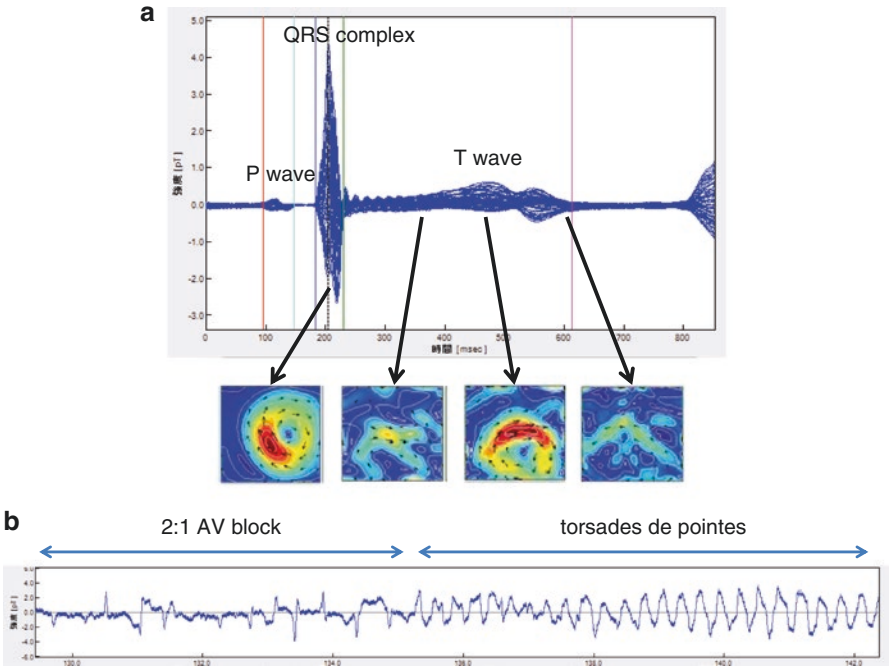

Fig. 18.3 Fetal magnetocardiography showing (**a**) accurate P-wave, PR interval, QRS interval, ST-T waves, QT interval, and RR interval evaluated using the signal-averaged method, and (**b**) consecutive recording of 2:1 atrioventricular (AV) block and torsades de pointes due to long QT syndrome

18.3 Management

18.3.1 Premature Contractions

Most fetuses evaluated for an irregular rhythm have a structurally normal heart with isolated premature contractions that disappear during pregnancy or shortly after birth. Premature atrial contraction (PAC) accounts for most patients with an irregular heartbeat at any age. PAC manifests as premature P-waves with abnormal P-wave axes and with an AV conduction that may be normal, aberrant, or blocked. In echocardiography, PAC is detected as a shorter than normal atrial interval. If AV conduction is normal, the premature atrial event is followed by a timely related premature ventricular event. If the PAC is premature enough to prevent conduction across the refractory AV node, no ventricular event is observed, which manifests as a skipped heartbeat. Before birth, PACs have been associated with a less than 1% risk of fetal tachyarrhythmias, although a higher risk has been suggested for atrial bigeminy and couplets [16]. PACs usually spontaneously resolve without medical treatment. Premature ventricular contraction (PVC) is uncommon in utero. PVC manifests in a premature QRS complex that is not preceded by a P-wave. In echocardiography, PVC is not preceded by an atrial beat, whereas atrial intervals are usually normal and regular. Isolated PVCs are typically benign and self-limited and require no treatment. PVCs secondary to ventricular aneurysm or cardiomyopathy should be noted. The American Heart Association statement recommends fetal echocardiography to assess cardiac structure and function and to determine the mechanism of arrhythmia if the fetus presents with frequent ectopic beats [17]. Fetal heart rate should be monitored weekly until PACs or PVCs have resolved.

18.3.2 Fetal Tachyarrhythmias

Detection of a fast heart rate >180 bpm in a fetus constitutes a medical emergency because it carries a significant risk of fetal heart failure, hydrops, and death. Possible mechanisms include SVT, AFL, and VT. SVT and AFL account for 90% of fetal tachyarrhythmias, and both are readily distinguished by echocardiography. Secondary sinus tachycardia due to hyperthyroidism should be excluded. A variety of fetal and maternal conditions may cause sustained sinus tachycardia, including distress, anemia, and infection. The underlying cause of tachycardia should be treated.

18.3.2.1 Atrioventricular Reentrant Tachycardia

Atrioventricular reentrant tachycardia (AVRT), the most common mechanism of fetal SVT, involves a reentrant circuit that uses the AV node to conduct from the atria to the ventricles and a fast-conducting accessory pathway to propagate the ventricular impulse back to the atria [18]. Heart rate in AVRT usually ranges from 220 to 300 bpm. AVRT starts suddenly with a PAC and terminates with AV block. Most hearts are structurally normal, but Ebstein's anomaly is a well-known

association with accessory pathways. Fetal echocardiography shows a short ventriculoatrial (VA) pattern because atrial contraction occurs soon after ventricular contraction (Fig. 18.1a). Because of the near simultaneous atrial and ventricular contractions, the AV valves are closed during atrial systole, and there is pronounced A-wave flow reversal in the precordial veins and ductus venosus. fMCG can detect a delta wave in utero if there is anterograde pathway conduction during sinus rhythm (Wolff-Parkinson-White syndrome). In retrospective studies, 40% of fetuses with AVRT presented with hydrops, and this was associated with perinatal mortality of 21–27%. In contrast, the rate of perinatal mortality was <5% for cases without hydrops. After delivery, medical treatment must be reassessed relative to the antiarrhythmic drug used in utero, the duration since the last recurrence, and the mechanism of clinical tachycardia. Prophylactic antiarrhythmic treatment is often used to prevent AVRT recurrence during the first 6 months or longer because approximately 50% of AVRT cases have recurrence in the neonatal period [2, 19].

18.3.2.2 Ectopic Atrial Tachycardia

EAT accounts for 10–15% of cases of fetal SVT. EAT is caused by automaticity and arises from an ectopic focus within the atria. Cardiotocography is useful for detection of unique heart rate changes with a "warm-up and cool-down" phenomenon [10]. Although EAT is usually 1:1, conduction delay with AV block may be seen. EAT is more refractory to pharmacological treatment than AVRT, resulting in congestive cardiomyopathy [20]. Short-term antiarrhythmic treatment is often required, but EAT usually resolves before 6 months of life.

18.3.2.3 Atrial Flutter

AFL accounts for 30% of fetal tachyarrhythmias and is often associated with accessory AV pathways and reentrant SVT [2]. AFL is sustained by a macro-reentrant circuit that is confined to the AV ring. The atrial rate of AFL usually ranges from 400 to 540 bpm, which is commonly associated with 2:1 AV conduction and a ventricular rate of 200–270 bpm (Fig. 18.2b). A normal ventricular rate is occasionally observed in AFL with slower 3:1 or 4:1 AV conduction. In the absence of structural heart disease, AFL is almost exclusively observed in fetuses during the third trimester or at birth. If AFL persists to birth, sinus rhythm can be restored by synchronized electrical cardioversion. Neonatal recurrence of AFL is uncommon and long-term treatment is rarely required [18].

18.3.2.4 Fetal Treatment for SVT and AFL

A randomized control study has not been performed, but there is a clear clinical consensus on the efficacy of maternal transplacental antiarrhythmic therapy for fetal tachyarrhythmias [17]. Rapid pharmacologic cardioversion to a normal sinus rhythm is most pressing for hydropic fetuses with incessant tachyarrhythmia. Possible medications to treat fetal SVT and AFL until birth include maternal digoxin, sotalol, or flecainide alone or in combination. Oral administration of antiarrhythmic agents is recommended. Direct treatment of the fetus by intramuscular

injection may have a role in more rapidly restoring sinus rhythm in the hydropic fetus, but experience with this route is quite limited. The goal of fetal treatment is establishment of sufficient sinus rhythm or heart rate to allow resolution of hydrops or ventricular dysfunction. Management of fetal tachyarrhythmias depends on gestational age, the presence and degree of fetal compromise, hydrops or other risk factors, and potential fetal and maternal risks of fetal therapy and early delivery.

A flowchart for decisions on treatment of fetal tachyarrhythmias at the National Cerebral and Cardiovascular Center is shown in Fig. 18.4. Pharmacological treatment is recommended for all but the near-term fetus with sustained SVT or AFL (occurring more than 50% of the time) or with fetal hydrops or cardiac dysfunction. In contrast, treatment of intermittent tachyarrhythmia (less than 50% of the time) is likely to include close observation because heart failure rarely develops [21]. The treatment protocol depends on fetal and maternal risk analysis, with little data to support a specific treatment protocol that is likely to be most effective and to carry the lowest risk. In most cases at our center, digoxin is used as first-line therapy, a combination of digoxin and sotalol as second-line therapy, and a combination of digoxin and flecainide as third-line therapy. Fetal treatment is continued until delivery, even when cardioversion has been achieved, because approximately 15% of fetal tachyarrhythmias recur in utero [18].

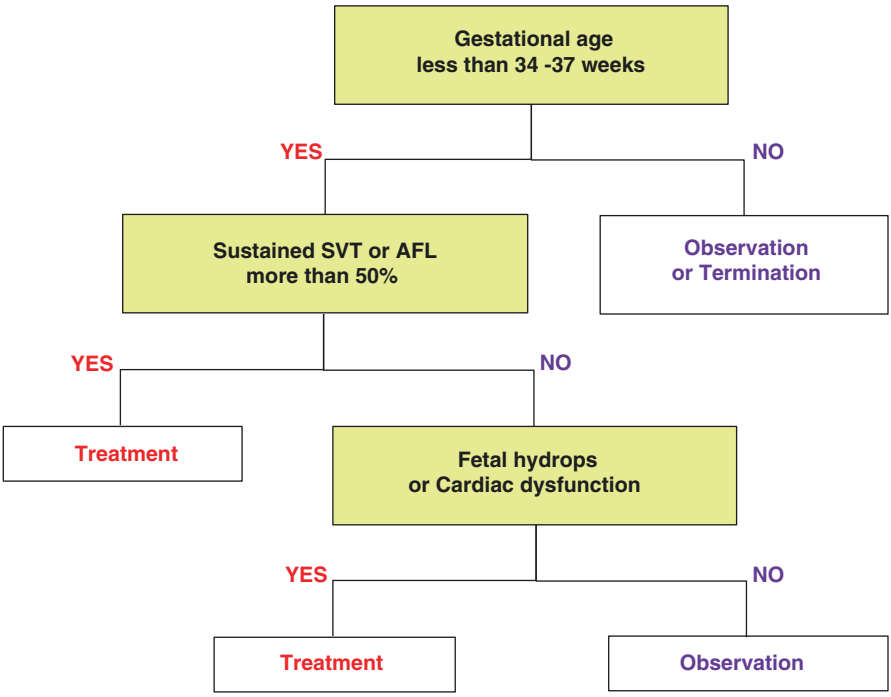

Fig. 18.4 Flowchart for decisions on treatment for fetal tachyarrhythmias at the National Cerebral and Cardiovascular Center. *SVT* supraventricular tachycardia, *AFL* atrial flutter

Fetal treatment as first- and second-line antiarrhythmic therapy is still controversial [22]. For reentrant SVT, maternal digoxin administered orally or intravenously is used as first-line therapy in many centers because of its relatively safe profile. In some centers, sotalol or flecainide is used as primary therapy [23–26]. For AFL, sotalol is recommended because it is effective in converting 50–80% of cases [24]. These agents are all reasonable as first-line choices, but there is no study indicating which the best initial therapy is. Sotalol, flecainide, and amiodarone have often been used as second-line therapy. However, amiodarone has a more significant toxicity profile for the mother and fetus and should be reserved as third-line treatment for life-threatening tachyarrhythmias [27, 28]. The duration of therapy with amiodarone should be minimized with discontinuation after hydrops resolve. There are no randomized, multicenter, clinical trials of use of antiarrhythmic agents in fetal tachyarrhythmias. Therefore, treatment protocols remain center specific. In Japan, a multicenter clinical trial using antiarrhythmic agents (digoxin, sotalol and flecainide) in fetal SVT and AFL has been done (UMIN000004270, http://en.fetusjapan.jp/).

18.3.2.5 Adverse Effects of Antiarrhythmic Medications

Relatively high doses of antiarrhythmic drugs are required during the second and third trimesters, since maternal circulating blood volume and renal clearance are both increased. There is limited information on maternal-fetal transfer of antiarrhythmic agents in humans. With the exception of sotalol and flecainide, most drugs have diminished transplacental transfer with fetal hydrops [29]. Nausea, fatigue, and loss of appetite are well-known adverse effects of digoxin, and sinus bradycardia or AV block are common effects or adverse effects with antiarrhythmic drugs. Use of combination therapies presents a greater risk of maternal and fetal complications than monotherapy. However, serious maternal adverse effects are rare in most reported series and generally resolve with discontinuation of therapy. For preventing proarrhythmia in the mother and fetus, it is important to keep the maternal serum potassium level at no less than 4.0 mEq/L. A maternal electrocardiogram is essential before treatment with QT-prolonging drugs such as sotalol, flecainide, and amiodarone, and close monitoring for maternal QTc interval is important. Frequent monitoring of drug levels and the maternal electrocardiogram are recommended to assess drug effects and toxicity, especially in dose escalation [17].

18.3.2.6 Ventricular Tachycardia

VT is a rare arrhythmia in fetuses. Fetal echocardiography shows tachycardia <200 bpm that is often incessant on presentation. VT often shows a short VA pattern similar to AVRT, which is most common in fetal arrhythmias. To distinguish VT from AVRT, close evaluation is important. The characteristic findings of VT are a ventricular rate higher than the atrial rate and dissociation between ventricular and atrial contractions. If fMCG shows a wide QRS in tachycardia, diagnosis of VT is more likely. In evaluation of fetal VT, possible causes include viral and anti-Ro antibody-mediated myocarditis, cardiac tumors, structural heart disease, and hereditary cardiomyopathy including long QT syndrome. Treatment and prognosis

depend on the VT mechanism and pattern, the hemodynamic impact, and associated conditions. Maternal intravenous magnesium is recommended as first-line treatment for fetal VT [30–32]. In addition, combination therapies of oral propranolol and mexiletine may be considered, even though there are no data showing which agent is most effective. In a case with suspected or confirmed long QT syndrome, drugs with QT-prolonging potential such as sotalol, flecainide, and amiodarone are contraindicated.

18.3.3 Fetal Bradyarrhythmias

Fetal bradyarrhythmias are defined by a heart rate <100 bpm. Occasional, brief sinus bradycardia is a benign physiologic response in which the rate of the sinus node is slower than normal for age. Prolonged or persistent bradycardia is of more concern and should trigger a more detailed assessment of the cause. The main mechanisms of fetal bradyarrhythmias include sinus bradycardia, complete AV block, and functional AV block due to nonconducted atrial bigeminy or long QT syndrome.

18.3.3.1 Sinus Bradycardia

Sinus bradycardia is defined as a rhythm that originates from the sinus node but in which the rate is slow for age. A subsidiary pacemaker may become the dominant pacemaker if the rate of the sinus node decreases to less than that of the secondary pacemaker. In echocardiography, fetal sinus or atrial bradycardia resembles that of a normal rhythm, with the only difference being that the atrial and ventricular rates are slow for gestational age, usually in the range of 80–110 bpm. Sinus bradycardia is well tolerated but may be secondary to fetal distress, sinus node dysfunction, and long QT syndrome. Perinatal management of sinus bradycardia depends on the underlying cause and may include no treatment, anti-inflammatory medication for myocarditis, and postnatal therapy.

18.3.3.2 Complete Atrioventricular Block

Complete AV block is defined as a complete failure of normal propagation of atrial impulses to the ventricles and is the most common congenital conduction abnormality before birth. Typical fetal echocardiography shows a regular normal atrial rhythm and rate, whereas the ventricles beat independently at a much slower rate of 40–80 bpm (Fig. 18.1c). In about half of fetal cases with congenital AV block, it is associated with major congenital heart defects (CHDs) such as left atrial isomerism and corrected transposition of the great arteries [33]. The prognosis of fetal bradyarrhythmia with CHD is still poor, with a nationwide survey in Japan showing neonatal and overall survival rates of 66% and 48%, respectively [3]. In fetal bradyarrhythmias associated with CHDs, a ventricular rate <55 bpm has significant effects on fetal myocardial dysfunction and fetal hydrops, resulting in a poor prognosis. However, all cases of corrected transposition of the great arteries or

ventricular rate ≥70 bpm survived. In the absence of structural heart disease, congenital AV block is strongly linked to the fetal transplacental passage of anti-Ro antibodies, which are prevalent in about 1–2% of pregnant women [34]. In 1–5% of exposed fetuses, the maternal antibodies lead to complications, including congenital AV block, sinus bradycardia, myocarditis, endocardial fibroelastosis, and dilated cardiomyopathy. Although fetuses with isolated congenital AV block often tolerate in utero circulation, the severe end of the disease spectrum includes low cardiac output, fetal hydrops, and death. Risk factors associated with perinatal death include gestational age, fetal hydrops, endocardial fibroelastosis, myocarditis, and ventricular rate <50–55 bpm [35, 36]. A nationwide survey in Japan showed that fetal hydrops was associated with a 14-fold increased risk of perinatal death, and myocardial dysfunction was a significant risk factor for a poor prognosis [37]. Interestingly, fetal heart rate and the presence of maternal antibodies were not associated with morbidity and mortality.

18.3.3.3 Fetal Treatment for Fetal Bradyarrhythmias

There is currently no consensus on the indications of fetal treatment for isolated congenital AV block, and there is no treatment available to reverse complete AV block [38]. Dexamethasone, intravenous immunoglobulin, beta-sympathomimetics, and postnatal pacing have been used to prevent or treat severe immune-mediated myocardial inflammation, to augment cardiac output, and to improve the prognosis [39, 40]. A flowchart of the decision protocol for fetal bradyarrhythmias in fetuses without CHDs at the National Cerebral and Cardiovascular Center is shown in Fig. 18.5. Treatment of congenital AV block depends on the origin, presence, and degree of heart failure and the ventricular rate. When signs of fetal hydrops,

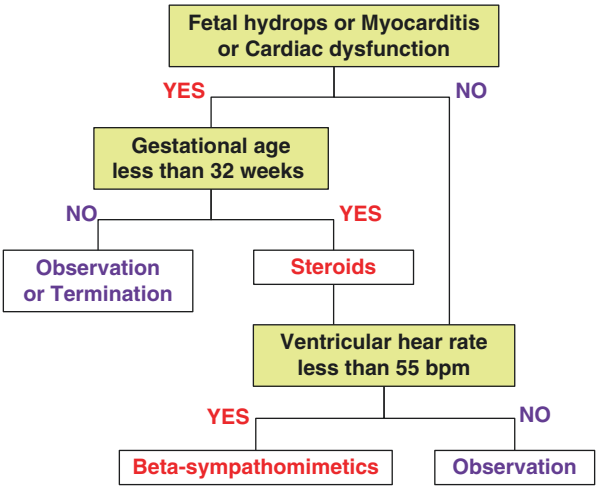

Fig. 18.5 Flowchart of the decision protocol for fetal bradyarrhythmias in fetuses without CHDs at the National Cerebral and Cardiovascular Center

myocarditis, pericarditis, or cardiac dysfunction are observed, maternal dexamethasone (4 mg/day for 2 weeks; 2 mg/day to 30 weeks of gestation; 1 mg/day to 31 weeks of gestation; 0.5 mg/day to 32 weeks of gestation) is used from the time of diagnosis to 32 weeks of gestation. When fetal hydrops or severe cardiac dysfunction develops after 34 weeks of gestation, neonatal treatment should be considered. Possible treatment-related adverse events that may preclude routine use of high-dose steroids include fetal growth restriction, oligohydramnios, and maternal diabetes mellitus and central nervous system side effects [39]. Chronic prenatal steroid therapy for congenital AV block has no obvious impact on neurocognitive function at school age [41]. However, it is recommended that steroid use is limited to <10 weeks to avoid maternal and fetal adverse effects, especially fetal growth restriction and oligohydramnios [37]. We also use transplacental ritodrine hydrochloride infusion (usually 30–200 μg/min) to maintain fetal ventricular heart rate at >55 bpm. However, recent studies have not shown efficacy of this treatment for fetuses with or without CHDs [10, 35–37]. Several reports have suggested addition of maternal intravenous immunoglobulin (1 g/kg every 2–3 weeks) if endocardial fibroelastosis and ventricular dysfunction are detected [40]. The optimal timing for administration and repeated dosing intervals is unknown. Prospective, randomized trials or a registry is needed to establish definitive treatment recommendations for a fetus with congenital AV block.

18.3.3.4 Long QT Syndrome

Long QT syndrome is an inherited ion channel disorder that manifests as several patterns of fetal arrhythmias [42, 43]. Sinus bradycardia is most common, usually in the range of 80–110 bpm. An irregular rhythm can also be caused by functional second-degree AV block (Figs. 18.1d and 18.3b), which is characterized by failure of AV conduction of atrial activity to the ventricle. Unlike in atrial bigeminy, the atrial rhythm in 2:1 AV block is fairly constant and 1:1 AV conduction recurs at slower atrial rates [16]. Long QT syndrome has the potential to cause VT or torsades de pointes (Fig. 18.3b), which is associated with fetal heart failure, hydrops, and sudden death, as in adults. Maternal intravenous magnesium is effective and recommended as first-line treatment for fetal VT or torsades de pointes due to long QT syndrome. Because of the predisposition of patients with long QT syndrome for VT-related cardiac arrests and sudden death, postnatal treatment with a long-acting beta-blocker with or without a pacemaker or implantable cardioverter-defibrillator is often required.

References

1. Saemundsson Y, Johansson C, Wenling S, Gudmundsson S (2011) Hepatic venous Doppler in the evaluation of fetal extrasystoles. Ultrasound Obstet Gynecol 37:179–183
2. Naheed ZJ, Strasburger JF, Deal BJ, Benson DW Jr, Gidding SS (1996) Fetal tachycardia: mechanisms and predictors of hydrops fetalis. J Am Coll Cardiol 27:1736–1740
3. Miyoshi T, Maeno Y, Sago H, Inamura N, Yasukouchi S, Kawataki M et al (2015) Fetal bradyarrhythmia associated with congenital heart defects - nationwide survey in Japan. Circ J 79:854–861

4. Gudmundsson S, Huhta JC, Wood DC, Tulzer G, Cohen AW, Weiner S (1991) Venous Doppler ultrasonography in the fetus with nonimmune hydrops. Am J Obstet Gynecol 164(1 Pt 1): 33–37
5. Hornberger LK, Sahn DJ (2007) Rhythm abnormalities of the fetus. Heart 93:1294–1300
6. Kleinman CS, Donnerstein RL, Jaffe CC, DeVore GR, Weinstein EM, Lynch DC et al (1983) Fetal echocardiography. A tool for evaluation of in utero cardiac arrhythmias and monitoring of in utero therapy: analysis of 71 patients. Am J Cardiol 51:237–243
7. Fouron JC, Fournier A, Proulx F, Lamarche J, Bigras JL, Boutin C et al (2003) Management of fetal tachyarrhythmia based on superior vena cava/aorta Doppler flow recordings. Heart 89:1211–1216
8. Nii M, Hamilton RM, Fenwick L, Kingdom JC, Roman KS, Jaeggi ET (2006) Assessment of fetal atrioventricular time intervals by tissue Doppler and pulse Doppler echocardiography: normal values and correlation with fetal electrocardiography. Heart 92:1831–1837
9. National Institute of Child Health and Human Development Research Planning Workshop (1997) Electronic fetal heart rate monitoring: research guidelines for interpretation. Am J Obstet Gynecol 177:1385–1390
10. Miyoshi T, Sakaguchi H, Katsuragi S, Ikeda T, Yoshimatsu J (2015) Novel findings of fetal ectopic atrial tachycardia by cardiotocography. Ultrasound Obstet Gynecol 46:629–630
11. Knudson JM, Kleinman CS, Copel JA, Rosenfeld LE (1994) Ectopic atrial tachycardia in utero. Obstet Gynecol 84:686–689
12. Leuthold A, Wakai RT, Martin CB (1999) Noninvasive in utero assessment of PR and QRS intervals from the fetal magnetocardiogram. Early Hum Dev 54:235–243
13. Horigome H, Takahashi MI, Asaka M, Shigemitsu S, Kandori A, Tsukada K (2000) Magnetocardiographic determination of the developmental changes in PQ, QRS and QT intervals in the foetus. Acta Paediatr 89:64–67
14. Stinstra J, Golbach E, van Leeuwen P, Lange S, Menendez T, Moshage W et al (2002) Multicentre study of fetal cardiac time intervals using magnetocardiography. BJOG 109:1235–1243
15. Zhao H, Strasburger JF, Cuneo BF, Wakai RT (2006) Fetal cardiac repolarization abnormalities. Am J Cardiol 98:491–496
16. Sonesson SE, Eliasson H, Conner P, Wahren-Herlenius M (2014) Doppler echocardiographic isovolumetric time intervals in diagnosis of fetal blocked atrial bigeminy and 2:1 atrioventricular block. Ultrasound Obstet Gynecol 44:171–175
17. Donofrio MT, Moon-Grady AJ, Hornberger LK, Copel JA, Sklansky MS, Abuhamad A, Cuneo BF et al (2014) Diagnosis and treatment of fetal cardiac disease: a scientific statement from the American Heart Association. Circulation 129:2183–2242
18. Krapp M, Kohl T, Simpson JM, Sharland GK, Katalinic A, Gembruch U (2003) Review of diagnosis, treatment, and outcome of fetal atrial flutter compared with supraventricular tachycardia. Heart 89:913–917
19. Gilljam T, Jaeggi E, Gow RM (2008) Neonatal supraventricular tachycardia: outcomes over a 27-year period at a single institution. Acta Paediatr 97:1035–1039
20. Wang JN, Wu JM, Tsai YC, Lin CS (2000) Ectopic atrial tachycardia in children. J Formos Med Assoc 99:766–770
21. Simpson JM, Sharland GK (1998) Fetal tachycardias: management and outcome of 127 consecutive cases. Heart 79:576–581
22. Jaeggi E, Öhman A (2016) Fetal and neonatal arrhythmias. Clin Perinatol 43:99–112
23. Oudijk MA, Michon MM, Kleinman CS, Kapusta L, Stoutenbeek P, Visser GH et al (2000) Sotalol in the treatment of fetal dysrhythmias. Circulation 101:2721–2726
24. Shah A, Moon-Grady A, Bhogal N, Collins KK, Tacy T, Brook M et al (2012) Effectiveness of sotalol as first-line therapy for fetal supraventricular tachyarrhythmias. Am J Cardiol 109:1614–1618
25. Jaeggi ET, Carvalho JS, De Groot E, Api O, Clur SA, Rammeloo L et al (2011) Comparison of transplacental treatment of fetal supraventricular tachyarrhythmias with digoxin, flecainide, and sotalol: results of a nonrandomized multicenter study. Circulation 124:1747–1754

26. Krapp M, Baschat AA, Gembruch U, Geipel A, Germer U (2002) Flecainide in the intrauterine treatment of fetal supraventricular tachycardia. Ultrasound Obstet Gynecol 19:158–164
27. Strasburger JF, Cuneo BF, Michon MM, Gotteiner NL, Deal BJ, McGregor SN et al (2004) Amiodarone therapy for drug-refractory fetal tachycardia. Circulation 109:375–379
28. Bartalena L, Bogazzi F, Braverman LE, Martino E (2001) Effects of amiodarone administration during pregnancy on neonatal thyroid function and subsequent neurodevelopment. J Endocrinol Invest 24:116–130
29. Ebenroth ES, Cordes TM, Darragh RK (2001) Second-line treatment of fetal supraventricular tachycardia using flecainide acetate. Pediatr Cardiol 22:483–487
30. Cuneo BF, Ovadia M, Strasburger JF, Zhao H, Petropulos T, Schneider J et al (2003) Prenatal diagnosis and in utero treatment of torsades de pointes associated with congenital long QT syndrome. Am J Cardiol 91:1395–1398
31. Horigome H, Nagashima M, Sumitomo N, Yoshinaga M, Ushinohama H, Iwamoto M et al (2010) Clinical characteristics and genetic background of congenital long-QT syndrome diagnosed in fetal, neonatal, and infantile life: a nationwide questionnaire survey in Japan. Circ Arrhythm Electrophysiol 3:10–17
32. Simpson JM, Maxwell D, Rosenthal E, Gill H (2009) Fetal ventricular tachycardia secondary to long QT syndrome treated with maternal intravenous magnesium: case report and review of the literature. Ultrasound Obstet Gynecol 34:475–480
33. Berg C, Geipel A, Kohl T, Breuer J, Germer U, Krapp M et al (2005) Atrioventricular block detected in fetal life: associated anomalies and potential prognostic markers. Ultrasound Obstet Gynecol 26:4–15
34. Jaeggi E, Laskin C, Hamilton R, Kingdom J, Silverman E (2010) The importance of the level of maternal anti-Ro/SSA antibodies as a prognostic marker of the development of cardiac neonatal lupus erythematosus a prospective study of 186 antibody-exposed fetuses and infants. J Am Coll Cardiol 55:2778–2784
35. Eliasson H, Sonesson SE, Sharland G, Granath F, Simpson JM, Carvalho JS et al (2011) Isolated atrioventricular block in the fetus: a retrospective, multinational, multicenter study of 175 patients. Circulation 124:1919–1926
36. Izmirly PM, Saxena A, Kim MY, Wang D, Sahl SK, Llanos C et al (2011) Maternal and fetal factors associated with mortality and morbidity in a multi-racial/ethnic registry of anti-SSA/Ro-associated cardiac neonatal lupus. Circulation 124:1927–1935
37. Miyoshi T, Maeno Y, Sago H, Inamura N, Yasukohchi S, Kawataki M et al (2012) Evaluation of transplacental treatment for fetal congenital bradyarrhythmia: - nationwide survey in Japan. Circ J 76:469–476
38. Saleeb S, Copel J, Friedman D, Buyon JP (1999) Comparison of treatment with fluorinated glucocorticoids to the natural history of autoantibody-associated congenital heart block: retrospective review of the research registry for neonatal lupus. Arthritis Rheum 42:2335–2345
39. Jaeggi ET, Fouron JC, Silverman ED, Ryan G, Smallhorn J, Hornberger LK (2004) Transplacental fetal treatment improves the outcome of prenatally diagnosed complete atrioventricular block without structural heart disease. Circulation 110:1542–1548
40. Trucco SM, Jaeggi E, Cuneo B, Moon-Grady AJ, Silverman E, Silverman N et al (2011) Use of intravenous gamma globulin and corticosteroids in the treatment of maternal autoantibody-mediated cardiomyopathy. J Am Coll Cardiol 57:715–723
41. Kelly EN, Sananes R, Chiu-Man C, Silverman ED, Jaeggi E (2014) Prenatal anti-Ro antibody exposure, congenital complete atrioventricular heart block, and high-dose steroid therapy: impact on neurocognitive outcome in school-age children. Arthritis Rheumatol 66:2290–2296
42. Cuneo BF, Strasburger JF, Yu S, Horigome H, Hosono T, Kandori A et al (2013) In utero diagnosis of long QT syndrome by magnetocardiography. Circulation 128:2183–2191
43. Cuneo BF (2015) The beginnings of long QT syndrome. Curr Opin Cardiol 30:112–117