

Preconception Counseling for Women with Congenital Heart Disease

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With advances that have been made over the recent decades in transcatheter and surgical interventions, most patients with congenital heart disease (CHD) can survive into adulthood. Overall, probably half of these surviving patients are female. When these female CHD patients reach childbearing age, however, pregnancy management will be a major issue. In order to meet the demands of fetal growth, the maternal cardiovascular system starts a series of adaptations beginning in early pregnancy. These adaptations include: decreased systemic and pulmonary vascular resistances, decreased blood pressure, expansion of the blood volume, increased heart rate and increased cardiac output. For women with CHD, this hemodynamic alteration may increase the risks of adverse cardiovascular events as well as the fetal and neonatal complications. Therefore, proper risk stratification and effective counseling for women with CHD who are planning their pregnancies is an important undertaking.

Key Words: Congenital heart disease • Pregnancy

INTRODUCTION

Due to the advances in treatment of congenital heart disease (CHD) in recent decades, it has been estimated that approximately 85% of patients with CHD can survive into adulthood.¹ Although many adults with CHD have received cardiac corrections, some of them still face problems such as heart failure, exercise intolerance, arrhythmias or even the risks of sudden death. Because of the increase in the population of CHD patients,² new and complex medical issues have posed great challenges for health care providers. Pregnancy in women with CHD is probably one of the most important of these issues. To meet the demands of fetal growth, the maternal cardiovascular system makes a series of adap-

tations such as decreased systemic and pulmonary vascular resistances, expansion of the blood volume, increases in heart rate and increased cardiac output. The presence of maternal CHD may increase the risk of maternal cardiovascular complications during pregnancy as well as the risk of fetal and neonatal complications owing to the altering hemodynamic status in pregnancy.³⁻⁶ Therefore, for women with CHD, the proper identification of risk and undertaking of counseling prior to planning pregnancy are therefore essential.⁷

CARDIOVASCULAR ADAPTATIONS DURING PREGNANCY

Hemodynamic changes during pregnancy

A reduction in peripheral vascular resistance begins at 5 weeks gestation as a consequence of developed uteroplacental circulation and increased circulating estrogen, progesterone and relaxin.⁸ The peripheral vascular resistance drops to 40-70% of pre-pregnancy levels at the middle of the second trimester.⁸ In response to the relative vascular underfill arising from decreased

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vascular resistance, an expansion in plasma volume (an increase of 30-50%), activation of the renin-angiotensin-aldosterone system and a mild reduction of plasma atrial natriuretic peptide concentration occurs to maintain a relatively constant blood pressure.^{8,9} The cardiac preload increases as a result of expansion of plasma volume, and the cardiac afterload decreases due to reduction of peripheral vascular resistance. These changes, together with an elevated heart rate 10-20/min, lead to an increased cardiac output to 30-50% above the pre-pregnancy level.¹⁰ To avoid excessive blood loss at delivery, hypercoagulation status is achieved by decreasing the production of tissue plasminogen activator, protein C and S and increasing tissue plasminogen activator inhibitor and factors V, VII, VIII, IX, X, XII and von Willebrand factor.¹¹

Labor, delivery and postpartum

Contraction of the uterus during labor can cause 300 to 500 ml of blood entering circulation. Heart rate and blood pressure may rise due to exertion, pain or anxiety. Therefore, cardiac output may increase as much as 80% above the pre-pregnancy level.¹² Although Cesarean delivery can eliminate or minimize hemodynamic stresses during labor, it is often associated with greater blood loss and greater fluid shifts than vaginal delivery. After delivery, increased cardiac preload by autotransfusion occurs after the return of uterine blood, decompression of inferior vena cava and reabsorption of the extracellular fluid. The hemodynamic adaptations to pregnancy usually take 4 to 12 weeks to return to baseline after delivery.¹³

MATERNAL COMPLICATIONS OF PREGNANCY IN WOMEN WITH CHD

The reported incidence of maternal cardiac complications associated with pregnancy in women with CHD ranges from 4.5 to 25.0%.³⁻⁷ These complications include heart failure, arrhythmia, thromboembolism, aortic dissection and pregnancy induced hypertension.

Heart failure

Volume expansions during pregnancy may further aggravate the impaired ventricular function by increased

cardiac preload. In patients with systemic right ventricle (such as congenitally corrected transposition of the great arteries or complete transposition of the great arteries after atrial switch operation), pre-existing right ventricle dysfunction may worsen; about 10-20% of these patients have an irreversible ventricular dysfunction after delivery.^{14,15} The increased cardiac output and reduction in peripheral resistance leads to an increase in the pressure gradient in patients with left heart obstructive lesions.

For patients with pulmonary arterial hypertension, lack of normal reduction in pulmonary vascular resistance during pregnancy can cause progressive right ventricular failure with increasing cardiac output.¹⁶ During delivery, patient pain and stress is associated with stimulation of the sympathetic nervous system and dramatic increases in the heart rate, blood pressure, and myocardial oxygen consumption, which can be associated with vagal responses potentially leading to hypotension and sudden death. Additionally, postpartum autotransfusion can cause further right ventricular volume overload.¹⁶ For those patients with Eisenmenger syndrome, in addition to the above complications related to pulmonary arterial hypertension, the reduced systemic vascular resistance and increased right ventricular volume overload lead to increased right to left shunting and aggravated cyanosis. A very high maternal mortality rate (30%) is associated with Eisenmenger syndrome and severe pulmonary arterial hypertension.¹⁷

Arrhythmias

The chances of arrhythmia increase during pregnancy due to enhanced sympathetic tone, alteration of hormone milieu and cardiac chamber dilatation. Such physiological changes may render a pre-existing substrate, such as reentry around the previous surgical scars, capable of sustaining an arrhythmia.¹⁸ Women particularly at risk are those having a previous history of arrhythmias, with complete transposition of the great arteries post atrial repair, after classical Fontan operation (atriopulmonary anastomosis) or atrioventricular septal defect.⁴

Thromboembolism

The presence of a hypercoagulable state during pregnancy and the disruption of lamina blood flow by

congenital or repaired cardiac defects can result in an increased risk of thrombosis and embolism.⁹ Patients with mechanical prosthetic valve, cyanosis, atrial fibrillation or Fontan circulation are especially at risk for thromboembolism. However, the use of anticoagulants is associated with risks of maternal or fetal bleeding and possible teratogenesis.

Aortic dissection

Elevation of estrogen and elastases during pregnancy results in fragmentation of the elastic lamella in the aortic wall media.¹⁹ The increased cardiac output and alteration of the aortic wall structure may increase the chances of aortic dissection during pregnancy, especially in patients with Marfan syndrome, bicuspid aortic valve, aortic coarctation, Ehlers-Danlos syndrome and Turner syndrome.

Pregnancy induced hypertension

The incidence of hypertension increases in patients with aortic stenosis, pulmonary stenosis, aortic coarctation and transposition of the great arteries.⁴ The larger pathophysiological mechanism is not clear, but endothelial dysfunction, impaired vascular dilatation, impaired systemic ventricle and release of vasoactive substances by the uterus may contribute to pregnancy induced hypertension in such patients.⁹

FETAL AND NEONATAL RISKS

In women with CHD, offspring complications are related to maternal cardiac function,⁵ especially those with maternal cyanosis or reduced cardiac output.²⁰ A recent study revealed that compromised uteroplacental blood flow is related to offspring events in women with CHD.²¹ The fetal and neonatal complications in maternal CHD include preterm delivery (10-20%), intrauterine growth retardation (8%), spontaneous abortion (12%) and Fetal/neonatal death (4%).^{3,4} The independent maternal predictors of neonatal events are baseline NYHA functional class > II or cyanosis, severe left heart obstruction, multiple gestation, use of anticoagulant during pregnancy and mechanical valve prosthesis.^{3,4,22} The overall recurrence rate of heart defects for offspring in maternal CHD is 6% (Table 1).²³ However, for those car-

diac defects associated with a genetic syndrome or single gene mutation (e.g. DiGeorge syndrome, Holt-Oram syndrome, Noonan syndrome), the risks of recurrent CHD would be up to 50%.

Cardiovascular drugs in pregnancy

Alteration of drug absorption, excretion, and bio-availability can occur during pregnancy. Consequently, dosage adjustment may be required due to altered drug distribution by increased intracellular and extracellular fluid and increased drug clearance related to elevation of renal perfusion and higher hepatic metabolism.²⁴ Most cardiovascular drugs can cross the placenta and expose the fetus to their pharmacological or embryopathic effects. Therefore, the benefits and risks for the mother and fetus have to be weighted carefully (Table 2).

PRE-CONCEPTION ASSESSMENT AND COUNSELING

For all women with CHD, counseling about future pregnancies and contraception should begin in adolescence to prevent accidental and potentially dangerous pregnancies. To obtain correct and complete information for risk stratification, a thorough evaluation should be performed including review of past medical records, assessment of current functional status, physical exami-

Table 1. Risk of recurrence in offspring of mother with congenital heart disease

Lesion	Risk of transmission (%)	No. of cases
Atrioventricular septal defect	11.6	5/43
Aortic stenosis	8.0	36/248
Coarctation	6.3	14/222
Atrial septal defect	6.1	59/969
Ventricular septal defect	6.0	44/731
Pulmonary stenosis	5.3	24/453
Patent ductus arteriosus	4.1	39/828
Tetralogy of Fallot	2.0	6/301
Total	5.8	222/3795

Data from Whittemore R, et al. 1994.²³

If a cardiac defect is associated with a genetic syndrome or single autosomal dominant gene mutation (e.g. DiGeorge syndrome, Holt-Oram syndrome, Noonan syndrome), the risks of recurrent cardiac defect would be up to 50%.

Table 2. Cardiovascular drugs in pregnancy

Relatively safe		Not safe		
Drugs	FDA category	Drugs	FDA category	Adverse effects
Adenosine	C	ACEI, ARB	D	Neonatal renal failure, IUGR, hypotension
β-blockers	C			
Calcium channel blockers	C	Warfarin	X	Fetal CNS & skeletal defect, intracranial hemorrhage
Digoxin	C			
Heparin	C	Amiodarone	D	Hypothyroidism and potential brain damage
Lidocaine	B			
Procainamide	C	Phenytoin	D	Fetal heart defects, IUGR, orofacial abnormalities
Quinidines	C			
Furosemide	C	Spironolactone	C	Anti-androgenic effect
Sildenafil	B			
Epoprostenol	B	Bosentan	X	Teratogenicity
Nitric oxide	C			

ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; CNS, central nerves system; FDA, U.S. Food and Drug Administration; IUGR, intrauterine growth retardation.

nations, pulse oximetry, electrocardiogram, imaging studies, cardiopulmonary exercise test and the use of Holter monitors. Cardiac catheterization is indicated when the information from non-invasive diagnostic tools is insufficient, such as pulmonary arterial hypertension or severity of obstructive lesions. The assessment and counseling should be performed by a well-trained adult CHD specialist.

Risk stratifications

The CARPREG investigators in Canada have provided a risk index for predicting maternal pregnancy outcomes in women with heart disease (74% of their study cohort were women with CHD).²² They defined four risk predictors: 1) prior cardiac event (heart failure, transient ischemic attack, stroke or arrhythmia); 2) a New York Heart Association (NYHA) functional classification > II or cyanosis at baseline; 3) impaired systemic ventricular function; and 4) severe left-sided heart obstruction. The estimated risks of cardiac events during pregnancy were 5%, 27% and 75% in those women with numbers of risk factors of 0, 1 and > 1, respectively (Table 3).

Another risk assessment, named the modified World Health Organization (WHO) risk classification, was recommended by the European Society of Cardiology (ESC) to estimate the risk of pregnancy in women with heart disease (Table 4).^{11,25,26} Four risk classes (WHO I, II, III and IV) were defined according to both specific heart lesions (e.g., Marfan syndrome, bicuspid aortic valve,

tetralogy of Fallot, aortic coarctation, Fontan circulation or systemic right ventricle) and the clinical cardiac status (e.g., systemic ventricular dysfunction). The categories ranged from the very low risk of WHO class I to the highest risk of WHO class IV, which was considered the contraindication for pregnancy. Our recent study and another prospective study both revealed that, compared with other risk estimation methods, the WHO classification demonstrated better performances in predicting the maternal cardiovascular risks in pregnancy.^{7,27}

For detailed lesion-specific risk assessment, the guidelines from the American College of Cardiology/

Table 3. Predictors of maternal cardiovascular events and risk score from the CARPREG study²²

CARPREG risk factors	
	<ul style="list-style-type: none"> • Prior cardiac event (heart failure, transient ischemic attack, stroke before pregnancy or arrhythmia). • Baseline New York Heart Association functional class > II or cyanosis. • Left heart obstruction (mitral valve area < 2 cm², aortic valve area < 1.5 cm², peak left ventricular outflow tract gradient > 30 mmHg by echocardiography). • Reduced systemic ventricular systolic function (ejection fraction < 40%).
No. of risk factors	Estimated maternal cardiac complications
0	5%
1	27%
2	75%

Table 4. Modified WHO classification of maternal cardiovascular risk^{11,26}

WHO I No significant risk elevation
<ul style="list-style-type: none"> • Uncomplicated, small or mild <ul style="list-style-type: none"> - pulmonary stenosis - patent ductus arteriosus - Mitral valve prolapse • Successfully repaired simple lesions (atrial or ventricular septal defect, patent ductus arteriosus, anomalous pulmonary venous drainage) • Atrial or ventricular ectopic beats, isolated
WHO II Mildly elevated risk
<ul style="list-style-type: none"> • Unoperated atrial or ventricular septal defect (no elevated pulmonary artery pressure) • Repaired tetralogy of Fallot (without relevant residua or sequelae) • Most arrhythmias
WHO II-III (depending on individual) Mildly to moderately elevated risk
<ul style="list-style-type: none"> • Mild left ventricular impairment • Hypertrophic cardiomyopathy • Native or tissue valvular heart disease not considered WHO I or IV • Marfan syndrome without aortic dilatation • Aorta < 45 mm in aortic disease associated with bicuspid aortic valve • Repaired coarctation
WHO III Significantly elevated risk
<ul style="list-style-type: none"> • Non-severe systemic ventricular dysfunction • Mechanical valve • Systemic right ventricle • Fontan circulation • Cyanotic heart disease (unrepaired without pulmonary hypertension) • Other complex congenital heart disease • Aortic dilatation 40-45 mm in Marfan syndrome • Aortic dilatation 45-50 mm in aortic disease associated with bicuspid aortic valve
WHO IV High risk (pregnancy contraindicated)
<ul style="list-style-type: none"> • Pulmonary arterial hypertension of any cause • Severe systemic ventricular dysfunction (LVEF < 30%, NYHA III-IV) • Previous peripartum cardiomyopathy with any residual impairment of left ventricular function • Severe mitral stenosis, severe symptomatic aortic stenosis, severe coarctation • Marfan syndrome with aorta dilated > 45 mm • Aortic dilatation > 50 mm in aortic disease associated with bicuspid aortic valve • Native severe coarctation

LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; WHO, World Health Organization.

American Heart Association,²⁸ the Canadian Cardiovascular Society²⁹ and ESC³⁰ have summarized the pregnancy suggestions according to specific congenital cardiac lesions.

Counseling after risk stratification

The cardiologist should sufficiently explain the estimated maternal and fetal risks to the patient, and arrange an individualized multi-disciplinary approach for future pregnancy (Figure 1).

1. If the patient has any correctable risk factors for maternal or fetal complications (e.g. left heart obstruction, cyanosis, arrhythmias), cardiac interventions for risk reduction should be performed before conception as possible to minimize the maternal and fetal events and to avoid the high risk of invasive intervention during pregnancy.
2. Current medications should be reassessed for possible harmful effects impacting the fetus during pregnancy. The cardiologist must discuss with the patient the benefits and risks of medication adjustment for the mother as well as the fetus.
3. When the patient possesses any uncorrectable risk factor that is contraindicated for pregnancy, it is exceedingly important for a consulting specialist to recommend an effective contraception method to prevent the high-risk pregnancy.
4. Genetic specialist counseling and recurrent risk estimation should be provided to all adults with CHD, regardless of the gender or severity of the cardiac condition. It is essential to obtain a detailed family history to pinpoint possibly affected members and identify possible dysmorphic clues relating to associated syndromes.
5. For women with higher risks for pregnancy, multi-disciplinary teams specializing in adult CHD management, including adult CHD specialist, obstetrician, anesthetist, genetic specialist and cardiac surgeon, should be available if necessary to provide optimal care during pregnancy.

SUMMARY

The hemodynamic burden of female patients during pregnancy may increase the cardiovascular risks in

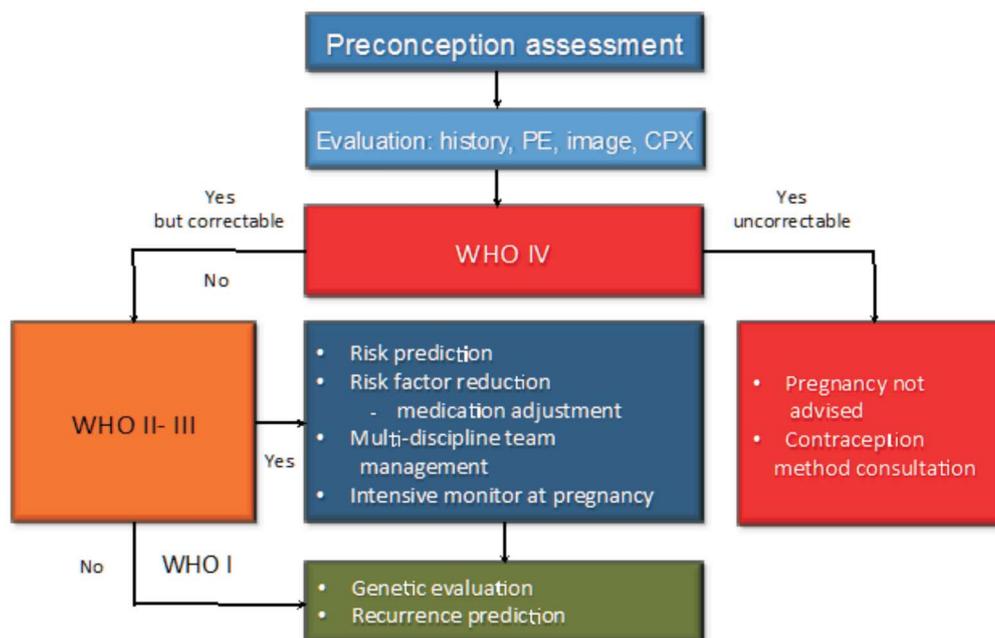


Figure 1. The flowchart for preconception assessment and counseling for women with congenital heart disease. CPX, cardiopulmonary exercise test; PE, physical examinations; WHO, World Health Organization.

women with CHD. Women with CHD who are considering pregnancy should receive adequate counseling and evaluation, which can further aid proper risk stratification.

DISCLOSURE

None of the authors have a conflict of interest.

REFERENCES

1. Warnes CA, Liberthson R, Danielson GK, et al. Task force 1: the changing profile of congenital heart disease in adult life. *J Am Coll Cardiol* 2001;37:1170-5.
2. Marelli AJ, Mackie AS, Ionescu-Ittu R, et al. Congenital heart disease in the general population: changing prevalence and age distribution. *Circulation* 2007;115:163-72.
3. Khairy P, Ouyang DW, Fernandes SM, et al. Pregnancy outcomes in women with congenital heart disease. *Circulation* 2006; 517-24.
4. Drenthen W, Pieper PG, Roos-Hesselink JW, et al. Outcome of pregnancy in women with congenital heart disease, a literature review. *J Am Coll Cardiol* 2007;49:2303-11.
5. Drenthen W, Boersma E, Balci A, et al. Predictors of pregnancy complications in women with congenital heart disease. *Eur Heart J* 2010;31:2124-32.
6. Balint OH, Siu SC, Mason J, et al. Cardiac outcomes after pregnancy in women with congenital heart disease. *Heart* 2010; 96:1656-61.
7. Lu CW, Shih JC, Chen SY, et al. Comparison of 3 risk estimation methods for predicting cardiac outcomes in pregnant women with congenital heart disease. *Circ J* 2015;79:1609-17. [Epub ahead of print]
8. Sanghavi M, Rutherford JD. Cardiovascular physiology of pregnancy. *Circulation* 2014;130:1003-8.
9. Karamermer Y, Roos-Hesselink JW. Pregnancy and adult congenital heart disease. *Expert Rev Cardiovasc Ther* 2007;5:859-69.
10. Ruys TP, Cornette J, Roos-Hesselink JW. Pregnancy and delivery in cardiac disease. *J Cardiol* 2013;61:107-12.
11. Kaleschke G, Baumgartner H. Pregnancy in congenital and valvular heart disease. *Heart* 2011;97:1803-9.
12. Harris IS. Management of pregnancy in patients with congenital heart disease. *Prog Cardiovasc Dis* 2011;53:305-11.
13. Capeless EL, Clapp JF. When do cardiovascular parameters return to their preconception values? *Am J Obstet Gynecol* 1991;165: 883-6.
14. Guedes A, Mercier LA, Leduc L, et al. Impact of pregnancy on the systemic right ventricle after a mustard operation for transposition of the great arteries. *J Am Coll Cardiol* 2004;44:433-7.
15. Gelson E, Curry R, Gatzoulis MA, et al. Pregnancy in women with a systemic right ventricle after surgically and congenitally corrected transposition of the great arteries. *Eur J Obstet Gynecol Reprod Biol* 2011;155:146-9.
16. Lane CR, Trow TK. Pregnancy and pulmonary hypertension. *Clin*

- Chest Med* 2011;32:165-74.
17. Weiss BM, Zemp L, Seifert B, Hess OM. Outcome of pulmonary vascular disease in pregnancy: a systemic overview from 1978 through 1996. *J Am Coll Cardiol* 1998;31:1650-7.
 18. Adamson DL, Nelson-Piercy C. Managing palpitations and arrhythmias during pregnancy. *Heart* 2007;93:1630-6.
 19. Immer FF, Bansi AG, Immer-Bansi AS, et al. Aortic dissection in pregnancy: analysis of risk factors and outcome. *Ann Thorac Surg* 2003;76:309-14.
 20. Gelson E, Curry R, Gatzoulis MA, et al. Effect of maternal heart disease on fetal growth. *Obstet Gynecol* 2011;117:886-91.
 21. Pieper PG, Balci A, Aarnoudse JG, et al. Uteroplacental blood flow, cardiac function, and pregnancy outcome in women with congenital heart disease. *Circulation* 2013;128:2478-87.
 22. Siu SC, Sermer M, Colman JM, et al. Cardiac Disease in Pregnancy (CARPREG) Investigators. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation* 2001;104:515-21.
 23. Whittemore R, Wells JA, Castellsague X. A second-generation study of 427 probands with congenital heart defects and their 837 children. *J Am Coll Cardiol* 1994;23:1459-67.
 24. Anderson GD. Pregnancy-induced changes in pharmacokinetics: a mechanistic-based approach. *Clin Pharmacokinet* 2005;44:989-1008.
 25. Thorne S, MacGregor A, Nelson-Piercy C. Risks of contraception and pregnancy in heart disease. *Heart* 2006;92:1520-5.
 26. 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, et al.; ESC Committee for Practice Guidelines. 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* 2011;32:3147-97.
 27. Balci A, Sollie-Szarynska KM, van der Bijl AG, et al. Prospective validation and assessment of cardiovascular and offspring risk models for pregnant women with congenital heart disease. *Heart* 2014;100:1373-81.
 28. Warnes CA, Williams RG, Bashore TM, et al. ACC/AHA 2008 Guidelines for the Management of Adults with Congenital Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines on the management of adults with congenital heart disease). *Circulation* 2008;118:e714-833.
 29. Silversides CK, Marelli A, Beaulac L, et al. Canadian Cardiovascular Society 2009 Consensus Conference on the management of adults with congenital heart disease. *Can J Cardiol* 2010;26:e65-150.
 30. Baumgartner H, Bonhoeffer P, De Groot NM, et al. Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of Cardiology (ESC); Association for European Paediatric Cardiology (AEPC); ESC Committee for Practice Guidelines (CPG). ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J* 2010;31:2915-57.

