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Pregnancy and Cardiovascular Disease (N Scott, Section Editor)

Pregnancy in Women with Congenital Heart Disease

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Opinion statement

Advances in cardiac surgical interventions in infancy and childhood have led to an increased number of women with congenital heart disease of childbearing age. For these women, individualized preconception counseling and pregnancy planning should be a vital component of their medical management, and presentation for obstetric care may even be an opportunity to re-establish cardiovascular care for patients who have been lost to follow-up. These patients have unique cardiovascular anatomy and physiology, which is dependent upon the surgical intervention they may have undergone during childhood or adolescence. These factors are associated with a variety of long-term complications, and the normal hemodynamic changes of pregnancy may unmask cardiac dysfunction and pose significant risk. Among three published risk assessment algorithms, the World Health Organization classification is the most sensitive in predicting maternal cardiovascular events in this population. Women with simple congenital heart defects generally tolerate pregnancy well and can be cared for in the community with careful monitoring. Conversely, women with complex congenital defects, with or without surgical repair and/or residual defects, should be managed in tertiary care centers under a multidisciplinary team of physicians experienced in adult congenital heart disease and high-risk obstetrics, who collaboratively participate in pregnancy planning, management, and care through childbirth and postpartum. Women who are cyanotic with oxygen saturation less than 85%, have significant pulmonary arterial hypertension of any cause, or have systemic ventricular dysfunction should be counseled to avoid pregnancy due to a very high risk of maternal and fetal mortality.

Introduction

Over the last two decades, one of the major improvements in cardiovascular medicine has been the advancement in early diagnosis and surgical management of patients with congenital heart disease (CHD), which has significantly increased the survival of patients with even complex congenital disorders well into adulthood. The prevalence of complex CHD in the adult population is estimated to be 3000 per million adults [1]. As a result, there are an increasing number of women with CHD seeking to bear children. Although maternal mortality is uncommon, cardiovascular causes account for over a third of cases and morbidity due to cardiovascular causes may be significant [2–5]. Careful planning and anticipation of issues may prevent these complications and minimize cardiac risk around the time of delivery and postpartum. Herein, we review the hemodynamic changes during pregnancy, risk stratification, general principles, and management of pregnant women with CHD based on the recently published American Heart Association (AHA) scientific statement on the management of pregnancy in patients with complex CHD and the European Society of Cardiology Guidelines on the management of cardiovascular diseases during pregnancy [6••, 7].

Hemodynamic changes of pregnancy and how it relates to women with CHD

During pregnancy, a number of physiological adaptations normally occur in order to supply the increased metabolic requirements of the mother and the fetus and to provide adequate placental perfusion. There is a 15–30% increase in heart rate (HR), which peaks in late second or early third trimester. While isolated rhythm disturbances in the form of supraventricular tachycardias are commonly seen among pregnant women with structurally normal hearts, patients with CHD may present with an increased burden of supraventricular or ventricular tachycardias, particularly in the setting of at-risk conditions such as tetralogy of Fallot, Fontan palliation or Ebstein's anomaly.

Preload is increased due to an increase in plasma volume and red blood cell (RBC) mass. The magnitude of increase in plasma volume is higher than the rise in RBC mass, which creates a relative anemia. Interestingly, this physiological anemia of pregnancy is beneficial in reducing the blood viscosity, aiding placental perfusion, and allowing for a lower cardiac work. While the rise in HR and stroke volume leads to a 30–50% increase in cardiac output, an increase in endothelial prostacyclin, relaxin, and nitric oxide production results in a reduced arterial stiffness and a decrease in total vascular resistance, with a relatively unchanged to only minimally reduced systolic blood pressure throughout pregnancy. All of these major hemodynamic shifts of pregnancy occur early in the second trimester (Fig. 1). Central venous pressure (CVP) and pulmonary capillary wedge pressure should remain normal throughout pregnancy [8].

During delivery, the cardiac output, pulmonary capillary wedge pressure, and CVP are augmented due to tachycardia and uterine contractions [9]. Uterine contractions and pain also elicit an increase in systemic arterial pressure and aortic wall stress. However, during the second stage of delivery, Valsalva maneuver causes a transient fall in venous return and cardiac output. In patients with critical obstructive lesions (i.e., aortic stenosis, mitral stenosis), pulmonary arterial hypertension, and limited stroke volume (such as

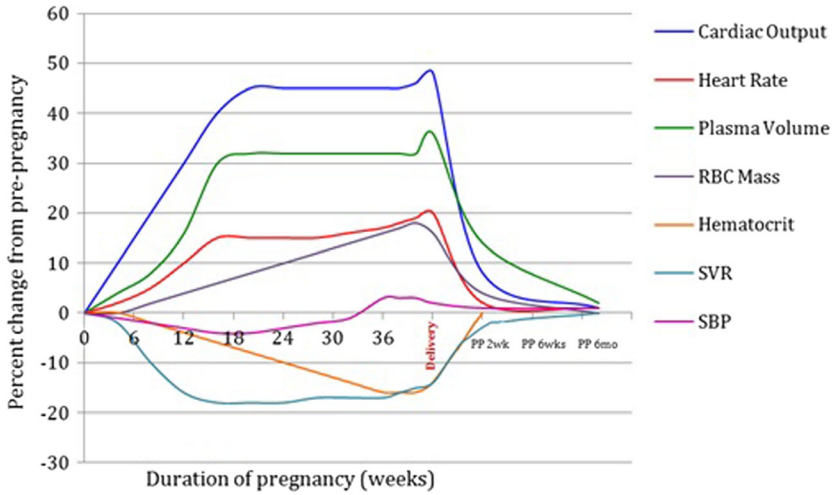

Fig. 1. Physiological adaptations in normal pregnancy. An increase in plasma volume and heart rate leads to a 30–50% increase in cardiac output. There is physiological anemia due to a larger rise in plasma volume than the red blood cell mass. Systolic blood pressure remains mostly unchanged due to a decrease in systemic vascular resistance. All major changes occur in the early second trimester and begin to normalize within 24–48 h and mostly return to baseline within 2 weeks post delivery. *RBC*—red blood cell, *SBP*—systolic blood pressure, *SVR*—systemic vascular resistance, *PP*—postpartum.

Fontan palliation), Valsalva maneuver may be avoided by passive fetal descent or utilizing forceps or vacuum extraction to assist and limit the second stage of delivery [10]. Immediately post delivery, as much as 500 ml of blood is sequestered back to the mother via the decompression of the inferior vena cava and expulsion of blood from the uterus.

Postpartum, the systemic vascular resistance begins to rise fairly abruptly and returns to pre-pregnancy levels around 2 weeks [11, 12]. Autotransfusion and rise in systemic vascular resistance may unmask myocardial dysfunction among women with susceptible systemic ventricles. Additionally, rises in systemic blood pressure may confer an increased risk of aortic dissection in patients with aortopathies. All physiological parameters begin to reverse within 24 h, returning to baseline in up to 6 months postpartum.

Preconception counseling, pregnancy planning, and risk stratification

Individualized preconception counseling is an essential part of the medical care given to women with CHD. Counseling should focus on the patient's clinical risk profile, including underlying anatomy and physiology that may increase pregnancy and delivery-related morbidity and the risk of genetic transmission of the CHD to the offspring. As many CHD patients may not be aware of their exercise limitations, quantification of aerobic capacity may be necessary [13]. Preconception functional capacity can be assessed with cardiopulmonary exercise testing, which may also unmask exercise-induced arrhythmias. Teratogenic medications such as angiotensin converting enzyme inhibitors and aldosterone receptor blockers should be discontinued. The anticipated delivery plan should include the patient, her

family, and the obstetric, cardiac, and anesthesiology teams. For most patients, vaginal delivery with epidural anesthesia is preferred. Cesarean delivery is reserved for obstetric indications and women with severe left or right ventricular dysfunction in New York Heart Association functional (NYHA) class III or IV, or aortic dissection, women who are on warfarin requiring urgent or emergent delivery, Eisenmenger physiology, and those with Marfan's syndrome and an aortic diameter >4.5 cm [6••, 7].

There are three commonly used algorithms to assess the individual risk of a patient. These risk stratification schemes are discussed in detail in another section of this journal issue. Out of these, modified World Health Organization (mWHO) classification recently has been shown to be the most reliable predictor of maternal cardiovascular complications when compared with CARPREG and ZAHARA [14].

Fetal risks are largely dependent on the maternal risk and the complexity of maternal CHD. The risk of CHD in the general population is 0.8%, whereas it is 3–8% in the offspring of women with CHD [15–17]. Men with CHD also have a greater risk of CHD in their offspring but less than that of women [15]. Therefore, all women with CHD, and those with male partners who have CHD, should be offered a fetal echocardiogram at 18–22 weeks of gestation [18].

General principles of pregnancy in women with CHD

Antibiotic prophylaxis

The American College of Obstretitians and Gynecologists recommends preoperative antiomicrobial prophylaxis for cesearean delivery to reduce postoperative maternal infectious morbidity [19]. On the other hand, the AHA and ESC guidelines do not support antibiotic prophylaxis for infective endocarditis during vaginal or cesarean delivery. Nevertheless, administration of antibiotics at the time of membrane rupture or prior to cesarean delivery may be considered for those at highest risk of an adverse outcome, such as patients with Eisenmenger syndrome, cyanosis, or prosthetic valves. Endocarditis prophylaxis is indicated for patients who have.

Genetic counseling

Genetic counseling is an integral part of risk stratification given the high risk of CHD in the offspring of women with CHD. Genetic evaluation should include a three-generation family history of CHD, with careful attention to the incidence of miscarriages. The AHA recommends genetic testing for all patients with clinical features of syndromic diseases, most of which are autosomal-dominant conditions with a transmission risk of 50%. These include Marfan, Holt-Oram, Noonan, Alagille, CHARGE (coloboma, heart defect, atresia choanae, retarded growth and development, genital abnormality, and ear abnormality), 22q11.2 microdeletion, and Williams syndromes. In addition, patients with CHD lesions associated with 22q11 deletion syndrome and/or DiGeorge syndrome, including Tetralogy of Fallot, interrupted aortic arch, truncus arteriosus, ventricular septal defect with aortic arch anomaly, isolated aortic arch anomaly, or discontinuous branch pulmonary arteries should be offered

genetic testing. A consensus statement published in 2013 by the Heart Rhythm Society also recommends genetic evaluation in the setting of maternal channelopathies and cardiomyopathies [20].

Cardiac surgery during pregnancy

Although maternal mortality associated with cardiopulmonary bypass is now similar to the mortality rate in non-pregnant women, fetal mortality rates of up to 33% have been reported [7, 21]. Therefore, cardiac surgery should be reserved for cases in which medical and interventional treatments are not adequate and should be delayed, if possible, to minimize the risk of fetal prematurity. If the gestational age is more than approximately 28 weeks, early delivery before cardiac surgery should be considered [7].

Left-sided lesions

Left heart obstruction

Congenital mitral valve stenosis (parachute mitral valve and supravalvular mitral ring) is uncommon and not amenable to percutaneous balloon valvuloplasty, and thus surgical correction should be performed prior to pregnancy among patients with severe obstruction. Congenital aortic valve disease mostly presents as bicuspid aortic valve with or without aortopathy. Pregnancy should be avoided in lieu of definitive treatment in symptomatic patients or asymptomatic patients with severe aortic stenosis and impaired left ventricular function, an abnormal exercise stress test with the development of arrhythmias, failure to augment systolic blood pressure (BP), or the development of myocardial ischemia or ventricular dysfunction, and/or an aortic root diameter >5.0 cm. Percutaneous balloon dilation may be utilized during the second or third trimester in pregnant women with symptomatic severe aortic stenosis who have amenable valve anatomy [22]. Early delivery via cesarean section followed by urgent surgical valve replacement may be required in cases of unfavorable valve anatomy. Cesarean delivery may be considered if the aortic root or ascending aorta diameter is increased significantly, or the aortic root measures >4.5 cm.

Patients with aortic coarctation carry a small risk of aortic dissection and an increased risk of pre-eclampsia and hypertension [7, 23, 24]. Women with unrepaired coarctation, and those with repaired coarctation with residual hypertension are at highest risk of aortic dissection and rupture of intracranial aneurysms [25]. Therefore, preconception screening is critically important in planning a safe pregnancy. In our practice, women with a coarctation gradient greater than 30 mmHg, or less than 30 mmHg with collateral vessels, symptoms of claudication or a significant drop in ankle brachial index in the preconception evaluation, are counseled to consider the risk versus benefit of coarctation revision prior to pregnancy. If these abnormalities are recognized during the pregnancy, cesarean delivery may be considered to decrease the risk of aortic dissection or aneurysm rupture [24]. In cases of hypertension, treatment with beta-blockers is recommended with careful titration to avoid placental hypoperfusion. It is important to note that upper extremity blood

pressure measurements overestimate the placental perfusion in patients with unrepaired or residual/recurrent coarctation.

Marfan syndrome

Marfan's syndrome is due to an autosomal-dominant mutation in the fibrillin-1 gene that results in abnormal connective tissue. Almost all patients have cardiac involvement with dilation of the aorta. There is contradicting data on the potential growth of the aorta during pregnancy. Rossiter et al. [26] and Donnelly et al. [27] found significant increase in aortic diameter during pregnancy in women with Marfan's syndrome, whereas Meijboom et al. [28] found no significant change. Aortic dissection most commonly occurs in the last trimester or the postpartum period. Most literature cites a 1% risk of dissection in women with aortic root diameter <4 cm which increases to 10% when the aortic root diameter exceeds 4 cm. More contemporary data suggests that patients who are being cared by cardiologists during pregnancy may have a lower risk of aortic dissection; however, numbers reported are too small to draw conclusion about rate of dissection in pregnancy [27]. Additionally, other fetal (small for gestational age, prematurity, fetal death) and obstetric complications (pre-eclampsia) are still very common [29]. Finally, Type B dissections have also been reported among peripartum women who have undergone ascending aortic repair [30] highlighting the fact that Marfan Syndrome remains a humbling disease in pregnancy and risk of dissection may not be completely eliminated by prophylactic aortic replacement. According to the WHO classification, women with aortic root diameter >45 mm are at the extreme high risk of maternal mortality or severe morbidity [31]. Based on the earlier data, the 2010 ACC guidelines recommend prophylactic ascending aortic replacement if the aortic root size is more than 40 mm in those who desire pregnancy [32]. European and Canadian guidelines are less stringent and report an aortic diameter of <45 mm to be considered safe during pregnancy with an increased long-term complication risk [33, 7]. Maintenance of normal BP and HR via beta-blocker therapy is most important to decrease the rate of dilation. Frequent imaging surveillance of the aorta during each trimester is reasonable in high-risk patients [32].

Right-sided lesions

Ebstein's anomaly

Ebstein's anomaly is a rare genetically heterogenous condition caused by the failure of delamination of the tricuspid valve leaflets from the underlying myocardium. This results in apical displacement of the septal and posterior leaflets, a variable degree of tricuspid regurgitation (TR), and a small true right ventricle (RV). Atrial septal defects, Wolf-Parkinson-White syndrome, and pulmonic stenosis may coexist. Asymptomatic women with normal oxygen saturation and no arrhythmias prior to pregnancy often have normal full-term vaginal deliveries but may require diuresis to avoid RV failure and arrythmias during pregnancy [34]. Patients with higher risk features, such as very small RV, significant TR, and history of tachyarrythmias may develop complications related to progressive RV failure from volume overload and a noncompliant myopathic RV. This

can lead to right-to-left shunting through an ASD causing cyanosis and risk for paradoxical embolization [35, 36]. Supraventricular arrhythmias can be treated with adenosine, verapamil, or cardioversion. Women with significant cyanosis (oxygen saturation <85%) or with symptomatic heart failure should be advised against pregnancy [35, 7, 6••].

Pulmonic stenosis

Modified WHO classification considers mild pulmonic stenosis as a very low-risk lesion for maternal cardiac complications. Nevertheless, non-cardiac complications are not uncommon. Drenthen et al. observed a high number of hypertension-related disorders (pre-eclampsia, eclampsia), premature deliveries, thromboembolic events, and recurrence of CHD in the offspring with an overall offspring mortality of 4.8% [37]. Although severe PS is generally well tolerated during pregnancy, in rare symptomatic cases in which medical therapy fails balloon valvuloplasty may be utilized [18, 7]. In the setting of severe pulmonic stenosis, regular cardiac physical examination and a serial echocardiographic evaluation for surveillance of RV function could be considered.

Tetralogy of Fallot

Tetralogy of Fallot, one of the most common CHD seen in women of childbearing age, comprises of RV outflow tract obstruction, ventricular septal defect (VSD), overriding aorta, and RV hypertrophy. The hemodynamic severity of the abnormalities depend upon the spectrum of RV outflow obstruction, ranging from mild infundibular obstruction to pulmonary atresia. Associated defects are common, such as ASD, patent ductus arteriosus, atrioventricular septal (endocardial cushion) defects, muscular VSD, anomalous pulmonary venous return, absent left pulmonary artery, aortic dilation with aortic regurgitation, and anomalous coronary arteries. Preconception evaluation for biventricular function, severity of pulmonic regurgitation, RV size, and arrhythmias is paramount for a safe pregnancy [38]. Asymptomatic women with severe pulmonic stenosis or residual RVOT obstruction, and those without ventricular dysfunction, prior arrhythmias or clinical right heart failure, tolerate pregnancy well. Conversely, women with moderate to severe pulmonary regurgitation (PR) and/or RV dilation are at risk of developing right heart failure during pregnancy [39]. A recent study showed a significant association between RV function parameters and uteroplacental Doppler flow suggesting that the decrease in cardiac function negatively impacts the placental perfusion, resulting in adverse neonatal outcomes [40]. Therefore, symptomatic women with severe PR and RV dilation should be considered for preconception pulmonic valve replacement [7, 39].

Shunt lesions

Atrial septal defect

Atrial septal defects (ASD) are generally well tolerated during pregnancy and delivery unless there is cyanosis, right-to-left shunt, or pulmonary arterial hypertension. However, given the theoretical risk of paradoxical embolism during the hypercoagulable state of pregnancy and the risk of pre-eclampsia, closure of the defect may be considered. A hemodynamically significant

secundum ASD with RV dilatation should be closed prior to pregnancy. Primum ASDs are often large, and can have an associated cleft mitral valve, with or without a ventricular septal defect (VSD). Sinus venosus ASDs are associated with partial anomalous pulmonary venous return and dilated RV. If unrepaired, meticulous leg care is important, compression stockings and heparin prophylaxis and early mobilization may be considered, as the reduction in systemic vascular resistance during the second trimester may promote increased right-to-left shunting. Some experts utilize low dose aspirin throughout pregnancy to prevent thromboembolic complications as it is quite safe [41]. Although there is no literature to support prevention in this population, aspirin has been shown to reduce venous thromboembolism in other populations [42]. Finally, atrioventricular septal defects are associated with worse outcomes when compared with simple ASDs. Deterioration of NYHA functional class, worsening of AV valvular regurgitation, and a high rate of offspring mortality due to the recurrence of complex CHD was reported by the ZAHARA investigators [16].

Ventricular septal defects

Although small defects are well tolerated, women with an unrepaired VSD are at increased risk of pre-eclampsia, and women with repaired VSD are at increased risk of premature labor and intrauterine growth retardation [43, 7]. Large unrepaired lesions may ultimately lead to pulmonary arterial hypertension and/or ventricular dysfunction, both of which pose an increased risk of adverse outcomes.

Eisenmenger syndrome/pulmonary arterial hypertension

Unrepaired large shunts may result in Eisenmenger syndrome, where there is an increased pulmonary vascular resistance secondary to a long-term increase in pulmonary flow, development of pulmonary vascular remodeling, and reversal of shunt flow from right to left with resultant cyanosis. A decrease in systemic vascular resistance during pregnancy results in a further increase in right-to-left shunting, with subsequent worsening of cyanosis, which contributes both to maternal and fetal risk.

Importantly, significant pulmonary arterial hypertension (PAH) of any cause carries a 30–50% risk of maternal and fetal mortality, and therefore is an absolute contraindication to pregnancy. The AHA and ESC both advise early termination of pregnancy in PAH, where dilation and evacuation procedures should be performed with assistance from an experienced cardiac anesthesiologist.

The prognosis of pregnant women with PAH depends on RV function and compliance. The inability of the RV to accommodate the increase in plasma volume and the lack of a decrease in pulmonary vascular resistance due to pre-existing pulmonary vascular disease is detrimental to maintaining cardiac output. Additionally, the prothrombotic state of pregnancy may predispose to in situ pulmonary thrombosis, further complicating the patient's hemodynamic status. Use of targeted pulmonary vasodilator therapy with prostaglandins and phosphodiesterase 5-inhibitors has been reported in small case series with favorable clinical outcomes [44, 45]. However, the mainstay of management of pregnancy in patients with PAH is supplemental oxygen, strict-bed rest in the third trimester with thromboembolic prophylaxis, and prolonged postpartum

hospital stay [6••]. There are no specific guidelines for the timing and mode of delivery, although many patients require a cesarean section due to hemodynamic decompensation.

Single ventricle physiology/Fontan circulation

Fontan palliation surgery is performed in patients with complex single ventricle physiology in order to direct the systemic venous return to the pulmonary arteries and separate deoxygenated and oxygenated blood. Long-term complications include systemic ventricular dysfunction, limited cardiac output, atrial arrhythmias, thromboembolic complications, hepatic and renal disease, baffle leaks, and cyanosis secondary to the development of systemic to pulmonary venovenous collaterals. The hemodynamic changes of pregnancy, hypercoagulable state, and decreased threshold for arrhythmias confer a high risk of fetal complications, such as premature birth, small for gestational age, and fetal mortality [7, 6••]. Furthermore, women with Fontan physiology have the highest rate of miscarriages and abortions [46, 7]. Preconception evaluation for ventricular function, intracardiac thrombus, and the risk of developing arrhythmias followed by serial echocardiogram in each trimester is recommended [6••]. In the setting of atrial arrhythmias during pregnancy, cardioversion to sinus rhythm may be required to reduce the risk of heart failure. Beta-blockers are the mainstay of treatment after cardioversion, whereas calcium channel blockers should be avoided due to their negative inotropic effects. Cesarean delivery is reserved for obstetric indications, and vaginal delivery with an assisted second stage and adequate regional anesthesia is recommended. During labor, the patient should be placed in the left lateral decubitus position to augment stroke volume [47, 6••]. Women who are on anticoagulation prior to pregnancy for any indication should be advised to continue anticoagulation with low molecular weight heparin.

Transposition of great arteries

D-TGA

D-transposition of the great arteries (D-TGA) is a cyanotic CHD where there is atrioventricular concordance and ventriculoarterial discordance. Original surgical correction was the atrial switch operation (Mustard or Senning), in which the venous circulation is diverted into the subpulmonic left ventricle and pulmonary circulation into a subaortic systemic RV. Potential long-term complications include atrial arrhythmias, baffle obstruction or leak, systemic AV valve regurgitation, and systemic RV dysfunction, all of which may be exacerbated during pregnancy. The AHA and ESC recommend against pregnancy when there is more than moderate systemic RV dysfunction, and ESC additionally recommends against pregnancy if there is severe systemic AV valve regurgitation. Some case series have reported worsening irreversible systemic RV dysfunction and systemic AV valve regurgitation in women who carried successful pregnancies [48, 49]. These results mandate a thorough discussion of patient risks with pregnancy in D-TGA.

The Jatene arterial switch procedure, where ventriculoarterial disconcordance is corrected and coronary vessels are reimplanted, was

introduced in the 1980s for patients with D-TGA and is now the preferred operation if feasible. Complications related to a systemic RV are eliminated; however, there is a risk of developing neoaortic dilation, aortic regurgitation, suprapulmonic stenosis, and coronary ostial narrowing resulting in ischemia. Although women who have undergone the Jatene procedure are expected to do well, there is scarce published data in regards to clinical outcomes [50, 51]. In a small retrospective study of nine women with 17 total pregnancies, one patient developed left ventricular systolic dysfunction and one a mechanical valve thrombosis [51].

L-TGA

L-transposition of the great arteries (L-TGA), also known as congenitally corrected transposition, is defined by atrioventricular discordance and a ventriculoarterial discordance, which results in a physiologically normal circulation with a systemic RV. Isolated cases often do not require surgical correction until later in life. Long-term complications are related to progressive failure of the systemic RV or associated repaired or unrepaired abnormalities such as VSD, pulmonic stenosis, anomalies of AV valves, and complete heart block. Atrial tachyarrythmias are commonly seen during pregnancy without any long-term complications [52]. Overall, women with a systemic RV are at a higher risk of cardiac complications including stroke, arrhythmias, congestive heart failure, cardiac arrest, or death during pregnancy [53].

Conclusion

In conclusion, preconception counseling is an essential part of care for women with CHD and should be initiated as early as possible. Pregnancy is well tolerated in women with simple CHD, whereas women with more complex CHD are at a higher risk of maternal and fetal cardiac and non-cardiac complications, and should have their delivery at an experienced tertiary care center. Women with cyanosis, pulmonary arterial hypertension, and Eisenmenger syndrome have the worst prognosis and should be advised against pregnancy. A thorough discussion of the risks and benefits of pregnancy and childbirth with the patient, a multidisciplinary team approach, anticipation of potential complications, and careful planning of pregnancy and delivery is required for optimal maternal and neonatal outcomes.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
his article does not contain any studies with human or animal subjects performed by any of the authors.

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