

Cardiovascular Disease in Pregnancy

Susan McIlvaine, MD,*† Loryn Feinberg, MD,† Melissa Spiel, DO†§

*Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

†Division of Cardiovascular Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

‡Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

§Department of Obstetrics, Gynecology, and Reproductive Biology, Harvard Medical School, Boston, MA

EDUCATION GAPS

1. The best management approach for timing and mode of delivery for pregnant women with cardiovascular disease needs to be understood.
2. Optimal fetal surveillance interval and modality in women with cardiovascular disease is still being understood.
3. Pregnancy may have some long-term effects on specific cardiovascular conditions.

OBJECTIVES *After completing this article, readers should be able to:*

1. Explain maternal cardiac physiology in pregnancy.
2. Describe specific cardiac conditions and how they are affected by pregnancy.
3. Review the effects of maternal cardiac disease on the fetus.
4. Recognize the importance of multidisciplinary care in caring for pregnant women with cardiovascular disease.

ABSTRACT

Cardiovascular disease remains a major contributor to rising maternal morbidity and mortality. Both the pregnant woman and fetus are exposed to many potential complications as a result of the physiologic changes of pregnancy. These changes can exacerbate existing cardiac disease, as well as lead to the development of de novo issues during gestation, delivery, and the postnatal period. For women with preexisting cardiac disease, including congenital malformations, valvular disease, coronary artery disease, and aortopathies, it is crucial that they receive multidisciplinary evaluation, counseling, and optimization before conception, as well as close monitoring and medication management during pregnancy. Close monitoring is also essential for patients who develop cardiovascular complications such as preeclampsia, cardiomyopathy, congestive heart failure, coronary events, and arrhythmias during pregnancy. In addition, concerning disparities in maternal morbidity and mortality exist across many dimensions, in part because of the lack of uniformity of care in different treatment settings. Establishment of multidisciplinary cardio-

AUTHOR DISCLOSURES Drs McIlvaine, Feinberg, and Spiel have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
AS	aortic stenosis
ROPAC	Registry of Pregnancy and Cardiac Disease
WHO	World Health Organization
ZAHARA	Pregnancy in Women with Congenital Heart Disease

obstetric teams including representatives from cardiology, anesthesia, obstetrics, maternal-fetal medicine, and specialized nursing has proven instrumental to delivering evidence-based and equitable care to high-risk patients. Multidisciplinary teams should work to guide these patients through the preconception, antepartum, delivery, and postpartum phases to ensure appropriate care for weeks to years after pregnancy.

INTRODUCTION

Maternal morbidity and mortality are rising in the United States, and cardiovascular disease is one of the leading causes of maternal mortality. (1)(2) In the United States, from 2014 to 2017, cardiovascular disease represented 33.6% of maternal mortality rates, with hypertensive disorders accounting for 6.6%, cardiomyopathy accounting for 11.5%, and other cardiovascular diseases accounting for 15.5% (Fig 1). While evolving methods of data collection may account for some of the increase seen in maternal morbidity and mortality, factors such as changing maternal demographics (ie, increased age) and a higher prevalence of preexisting comorbidities have contributed to the actual increase noted. (2) Data from the National Inpatient Sample have shown that the number of women with preexisting cardiovascular disease presenting for delivery

increased by almost 25% from 2003 to 2012. Over the same period, the prevalence of major adverse cardiac events increased by 18.8%. (3) In developed countries, women with congenital heart disease comprise a large proportion of women with preexisting cardiac disease; in contrast, in developing countries, acquired rheumatic heart disease contributes to the largest proportion of cardiac disease in pregnancy. (4) Although women with congenital heart disease represent a large group of those pregnant patients who have preexisting heart disease, they are not equally represented in major adverse cardiac events. (3) Instead, women with cardiomyopathy have the most adverse cardiac events. (3) The rationale for this remains unclear but may be related to cardiac optimization by the pregnancy team in the setting of known congenital heart disease, whereas women with cardiomyopathy, especially

Causes of Pregnancy-Related Death in the United States 2014 - 2017

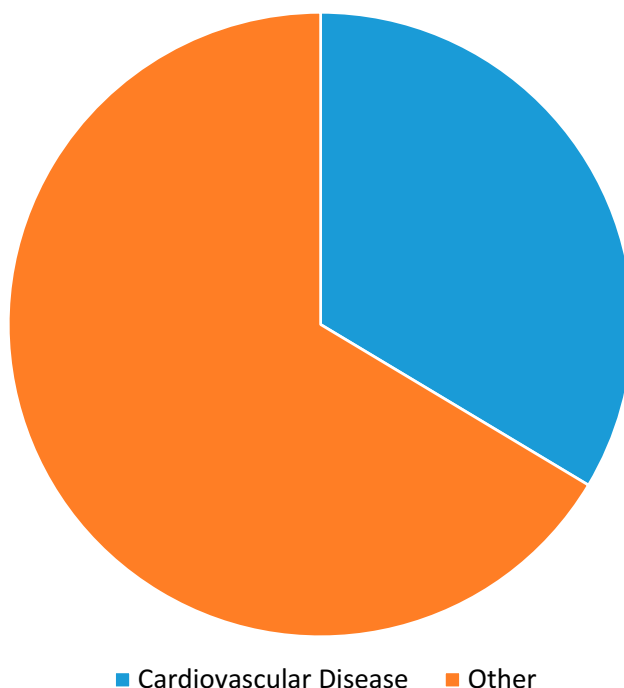


Figure 1. Adapted from the Centers for Disease Control and Prevention maternal mortality surveillance data. Blue=cardiovascular disease (includes hypertensive disease, cardiomyopathy, and other cardiovascular conditions), which in total made up 33.6% of pregnancy-related deaths in this period; orange=all other causes of death (infection, hemorrhage, thromboembolism, cerebrovascular events, amniotic fluid embolism, anesthesia complications, and other causes).

peripartum cardiomyopathy, often receive optimal cardiac care only after diagnosis, as they may not have had any prior indication to be followed by cardiac specialists.

As mentioned previously, cardiovascular disease remains a major contributing factor for maternal morbidity and mortality. In addition, these adverse outcomes are disproportionate across race, socioeconomic status, rural versus urban environment, hospital level, and country of origin. The foundation of these disparities is in place even before conception. In a recent cross-sectional study of more than 45 million live births over an 11-year period in the United States, prepregnancy hypertension almost doubled in both rural and urban women and remained about 20% higher in women who lived in rural areas. (5) In both rural and urban areas, rates of prepregnancy hypertension are highest for non-Hispanic black women. (5) The discrepancy among rates of pregnancy-related deaths is shown in Fig 2. Some of the disparities in outcomes can be attributed to access to specialty care and high-level hospitals, as women who deliver at tertiary care hospitals have lower rates of “preventable” complications. (6)(7) In addition, based on the Registry of Pregnancy and Cardiac Disease (ROPAC) data, developed countries also seem to have a lower maternal mortality rate compared with developing countries, at 0.6% versus 3.9%, respectively. (4) Between-country differences are also notable, especially in the prevalence of peripartum cardiomyopathy. As an

example, the incidence of peripartum cardiomyopathy is 1 in 100 pregnancies in Nigeria and 1 in 299 pregnancies in Haiti, compared to an incidence of 1 in 10,000 pregnancies in Denmark. (8) These disparities further complicate optimal treatment of women with cardiovascular disease in pregnancy.

To reduce the disparities that exist and manage the changing maternal demographics, including increasing comorbid conditions, a multidisciplinary cardio-obstetric care team may play a crucial role in delivering equitable maternity care for women with medical complications. Among women who have preexisting cardiac disease and have experienced serious cardiac events, almost half were deemed “preventable” and related to “inadequacies” in provider management. (7) Implementation of a multidisciplinary cardio-obstetric care is one strategy to address some of these issues, as the goals of this team are to review patients together, discuss medications and treatments, and provide management decisions during the antepartum, intrapartum, and postpartum period. This multidisciplinary cardio-obstetric care team should include specialists in cardiology, anesthesia, obstetrics and maternal-fetal medicine, nursing, and if indicated, pharmacy, neonatology, social-work, case management, and genetics. (9)

Ideally, this multidisciplinary team will also review cardiac risk assessment before conception or as soon as

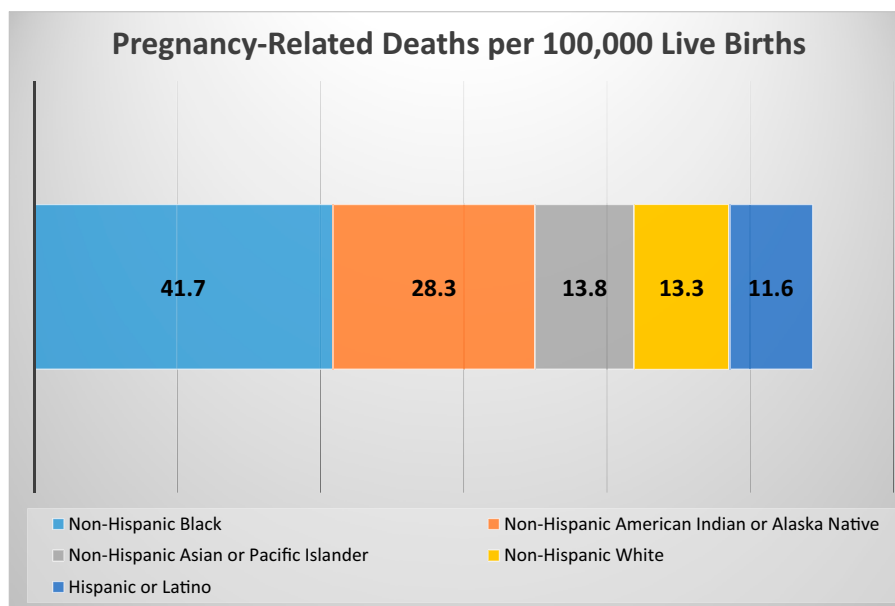


Figure 2. Adapted from the Centers for Disease Control and Prevention data on maternal mortality ratio by race/ethnicity from 2014 to 2017. Non-Hispanic black women experience the highest mortality per 100,000 live births, followed by non-Hispanic American Indian, Pacific Islander, non-Hispanic white, and Hispanic or Latino women. Light blue=non-Hispanic Black (41.7/100,000 live births); orange=non-Hispanic American Indian or Alaska natives (28.3/100,000 live births); grey=non-Hispanic Asian or Pacific Islander (13.8/100,000 live births); yellow=non-Hispanic white (13.4/100,000 live births); dark blue=Hispanic or Latino (11.6/100,000 live births).

conception is confirmed. Risk assessment can be derived from the patient's functional status, using New York Heart Association class, as well as the knowledge derived from several key studies evaluating outcomes for pregnant women with cardiac disease. Predictors of cardiac events in pregnant women are included in Fig 3. Regardless of which strategy is used for risk classification, it is important for the pregnancy cardiac team to recognize the limitations of the strategy used.

PHYSIOLOGIC CHANGES DURING NORMAL PREGNANCY AND THE PUERPERIUM

In a normal pregnancy, changes in maternal hemodynamics occur to ensure adequate fetal development and respond to an increased maternal metabolic demand. Cardiac output increases to meet these demands through increased blood volume, increased heart rate, and decreased peripheral vascular resistance. These hemodynamic changes have implications for both existing cardiac disease and the development of pregnancy-related cardiovascular complications.

Total blood volume begins to increase early in the first trimester, driven primarily by an increase in plasma volume, along with a proportionally smaller increase in red blood cell mass, (10) resulting in physiologic anemia. Heart rate peaks in the late third trimester, at around 25%

above prepregnancy values. (11) The upper limit of a normal resting heart rate has been shown to be approximately 115 beats/min. (12) Most of the aforementioned physiologic changes are well tolerated in pregnancy, but for women with cardiac disease, this is not always the case.

In addition to the physiologic changes in the antepartum period, cardiocirculatory changes occur during labor and delivery. During labor, there is a catecholamine surge that contributes to increased heart rate and myocardial contractility, and the contracting uterus contributes to increased blood volume and venous return to the heart. (13) If a pregnant woman were to undergo a cesarean delivery, there are also hemodynamic shifts that need to be considered and often relate to maternal positioning and the type of anesthesia provided, whether local, general, or regional analgesia.

During the immediate postpartum period, major hemodynamic changes occur, including increased cardiac output and stroke volume by greater than 50%, mostly due to the autotransfusion of blood from the contracting uterus and relief of inferior vena cava compression from the gravid uterus, leading to an increase in venous return. (14) As early as 1 hour after delivery, heart rate and cardiac output return to prelabor values. Notably, many physiologic changes of pregnancy persist up to 6 to 12 weeks after delivery, highlighting the importance of ongoing care in the extended postpartum period.

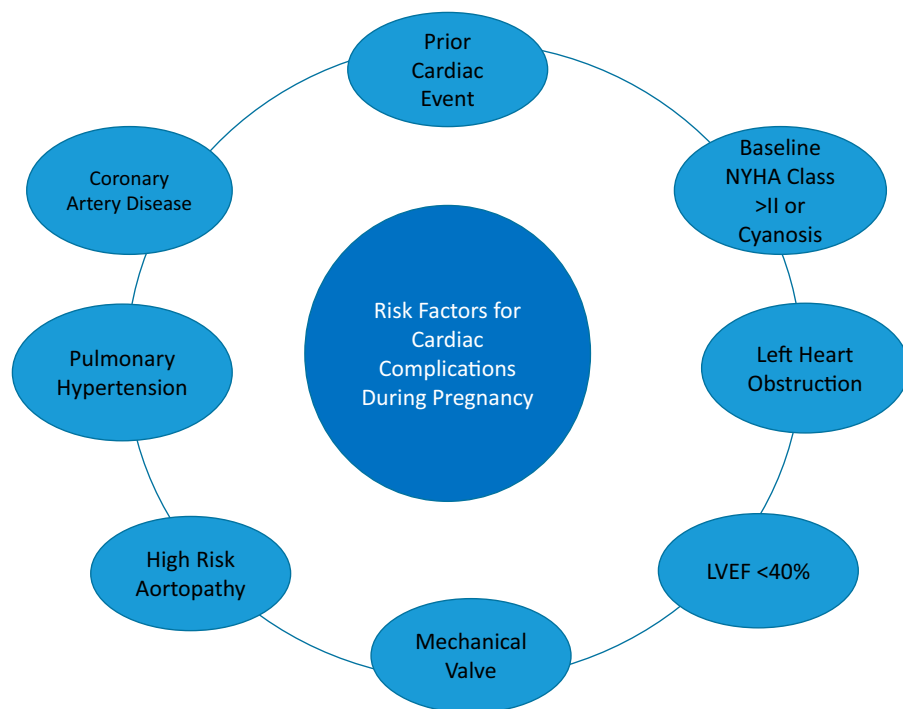


Figure 3. Risk factors for cardiac complications during pregnancy. Adapted from Silversides CK, Grewal J, Mason J, et al. Pregnancy outcomes in women with heart disease: the CARPREG II Study. *J Am Coll Cardiol*. 2018;71(21):2419–2430. (27)

PREEXISTING CARDIAC DISEASE

Congenital Cardiac Disease

Because of improvements in care, most women with congenital heart disease survive to reproductive age. (15) The spectrum of congenital heart disease is quite broad, and spans from a small atrial septal defect to much more complex lesions such as tetralogy of Fallot. Accordingly, the risk of pregnancy varies significantly with the type of congenital defect. For example, a woman with a repaired atrial septal defect is considered a modified World Health Organization (WHO) pregnancy risk category I, with no detectable increase in risk, whereas a woman with severe unrepaired aortic coarctation is considered modified WHO pregnancy risk category IV and should be advised against pregnancy. (15) In terms of adverse maternal outcomes in women with congenital heart disease, heart failure and arrhythmia are the most common maternal cardiac complications. Depending on the cohort of women studied, preterm birth varied from 10% to 20%. (16)(17)(18) In pregnancies complicated by congenital heart disease, the incidence of a small-for-gestational age neonate was 15% to 20%, with a 1% to 4% risk of fetal and neonatal death. (16)(17)(18)

Valvular Disease

For women of childbearing age, valvular lesions are often congenital or secondary to rheumatic heart disease. The hemodynamic changes associated with pregnancy can be quite burdensome for women with valvular disease. Among pregnant women, the most common valvular lesions worldwide are mitral stenosis and regurgitation, followed by aortic valve disease. (4) In general, regurgitant lesions are better tolerated in pregnancy than stenotic lesions, but the risks vary, depending on the type and severity of valve disease as well as the presence of any additional cardiac abnormalities. With stenotic lesions, increased cardiac output will lead to escalating transvalvular gradients throughout pregnancy, whereas regurgitant lesions may benefit from the physiologic reduction in systemic vascular resistance. A preconception evaluation should include quantification of functional capacity, assessment of the severity of the valve lesion, determination of the function of both ventricles, and estimation of pulmonary artery pressures. In women who have severe valvular disease but are asymptomatic, exercise testing with a treadmill stress test or cardiopulmonary exercise test should be considered to help decide whether any prepregnancy intervention is necessary. (19)

If valvular intervention is indicated, this should be performed before conception, with careful consideration of the choice of bioprosthetic or mechanical valve and the implications for future pregnancies. The bioprosthetic valves have been associated with more favorable pregnancy outcomes and less risk of thrombosis or hemorrhagic events. (20) Mechanical valves require therapeutic anticoagulation, and some experts favor warfarin as it is associated with the lowest risk of valve thrombosis. However, warfarin confers a risk of fetal teratogenicity, which in some studies has been associated with daily dosages above 5 mg. To avoid the risks of warfarin embryopathy, its use is often avoided in the first trimester and instead low-molecular-weight heparin or unfractionated heparin may be used. Warfarin use may be restarted after the first trimester and then again discontinued around 1 week before delivery to avoid bleeding complications in the puerperium. The transition between warfarin and heparin should be made in the inpatient setting with careful monitoring. If valve intervention does not occur before conception and becomes indicated in pregnancy, such as when a patient is hemodynamically unstable or has severe symptoms refractory to medical management, the risks of intervention are unpredictable, especially for the fetus. (19) The risk to the fetus is highest if surgical intervention, such as surgical valve replacement or repair, is needed.

Severe aortic stenosis (AS) in pregnancy is commonly caused by a congenitally bicuspid aortic valve. Although mild and moderate AS are generally well-tolerated during pregnancy, severe AS carries significant maternal and fetal risks. In the ROPAC cohort, 42% of women with severe symptomatic AS were hospitalized for cardiac reasons during pregnancy, 26.3% of women experienced heart failure during pregnancy, and low birthweight was more common among children born to mothers with severe AS. Overall, compared to patients with moderate AS, patients with severe AS had a 2.8-fold greater risk of maternal complications and a 7.6-fold greater risk of fetal complications. (21)

Mitral disease is often acquired from rheumatic heart disease, which is more prevalent in developing countries. The normal physiologic changes of pregnancy predispose women with mitral stenosis to pulmonary edema and atrial fibrillation. In the ROPAC cohort, 23.1% of women with mitral stenosis required hospital admission during pregnancy for a cardiac reason, and 49.1% of women with severe mitral stenosis experienced heart failure. β -blockers and diuretics are the mainstays of treatment. If atrial fibrillation occurs, therapeutic anticoagulation with heparin or warfarin is recommended. (22)

Mitral regurgitation is generally better tolerated than mitral stenosis in pregnancy, but it is not without risk. Among women in the ROPAC cohort, 20% with moderate to severe mitral regurgitation required hospitalization for a cardiac reason and 23% developed heart failure. (20)

Aortopathies

In women with aortopathies, the most catastrophic and potentially fatal complication for both the pregnant woman and fetus is aortic dissection. (23) Hemodynamic changes of pregnancy increase aortic wall stress, while hormonal changes in pregnancy increase remodeling of the tunica media and intima of the aorta, both of which increase the risk of dissection. (24) Up to half of all aortic dissections and ruptures in women younger than 40 years are associated with pregnancy. (25) The third trimester and postpartum periods are the most common points when dissection occurs, likely in part related to peak cardiac output and maximal root diameter. (26) Women with Marfan syndrome, bicuspid aortic valve with aortic dimension greater than 45 mm, Loeys-Dietz syndrome, vascular Ehlers-Danlos syndrome, and prior aortic dissection are among those most at risk for adverse pregnancy outcomes. (27) To best counsel and identify women at risk, preconception magnetic resonance imaging of the entire aorta is advised. (22) Pregnancy is contraindicated for some women in the high-risk category for dissection.

During pregnancy, medical management should focus on blood pressure and heart rate control with labetalol or metoprolol. Per European Society of Cardiology guidelines, echocardiography of the aorta should be performed every 4 to 12 weeks during gestation. (22) If serial screening reveals progressive dilation of the aorta, surgical treatment during pregnancy should be considered. If the fetus is viable, cesarean section followed by aortic surgery is recommended. Ideally, regional anesthesia is used for cesarean delivery, and the goal is to avoid prolonged labor and Valsalva maneuver. Generally, cesarean section should also be considered when the aorta diameter is greater than 45 mm. If a dissection of the ascending aorta (type A) occurs in pregnancy, this is an emergency that warrants immediate surgery. Management of the fetus depends on the gestational age, but if the fetus is viable and greater than 28 weeks' gestation, cesarean delivery is recommended, followed by immediate cardiac surgery. If the fetus is viable and is at less than 28 weeks' gestation, aortic surgery can be performed with continuous fetal monitoring, but carries with it an increased and unpredictable risk of fetal loss. (28) In contrast, dissections of the

descending aortas (type B) can typically be managed medically with aggressive blood pressure and heart rate control. (22) β -adrenergic agents such as metoprolol, propranolol, and atenolol are often used for heart rate control, and nitroglycerin, sodium nitroprusside, and hydralazine are used for blood pressure control at the lowest values that will allow for adequate placental perfusion. (13)(29) Some of the fetal effects of these medications are listed in the Table. Even with the use of high doses of sodium nitroprusside, maternal thiocyanate toxicity is rarely encountered, if the medication can be used for short periods. Prompt response to warning signs of dissection, early intervention, and multidisciplinary care are vital to successful pregnancy outcomes.

ACQUIRED CARDIAC DISEASE

Hypertensive Disorders

Hypertensive disorders of pregnancy are common and according to the Centers for Disease Control and Prevention, approximately 9.3% of reproductive-age women have hypertensive disease. (30) Unfortunately, many women are unaware of this diagnosis and approximately 40% have uncontrolled hypertension. (30) Given that hypertensive diseases are associated with many adverse outcomes in pregnancy, such as stroke, preeclampsia, fetal growth restriction, placental abruption, pulmonary edema, chronic kidney disease, and maternal or fetal mortality, it is imperative that women seek care and are optimized as early as possible in pregnancy or ideally during the preconception period.

Generally, hypertension is defined by at least 2 measurements of systolic blood pressure greater than or equal to 140 mm Hg or diastolic blood pressure greater than or equal to 90 mm Hg, or when participants reported currently using medication to lower blood pressure before conception or during the first 20 weeks of pregnancy. However, new recommendations advised initiation of treatment in nonpregnant adults with risk factors for current or future cardiovascular disease in patients with stage 1 hypertension (systolic blood pressure of 130–139 mm Hg or diastolic blood pressure of 80–89 mm Hg). (31) In pregnancy, to preserve placental perfusion while limiting maternal risk, goal blood pressures are ideally kept between 120 and 160 mm Hg systolic and between 80 and 105 mm Hg diastolic. If antihypertensive agents are required, medications that are commonly used include nifedipine, labetalol, methyldopa, or hydralazine. Antihypertensive agents have not been shown to reduce adverse outcomes to the fetus, (32) but are beneficial at

Table. Cardiac Medications and the Fetal Effects in Pregnancy

Fetal Effects	Cardiac Medications
No adverse fetal effects	• Adenosine • Amlodipine (limited human data, animal data suggest risk) • Digoxin • Diltiazem • Dopamine • Dobutamine • Epinephrine (when used acutely) • Ephedrine (when used acutely) • Enoxaparin • Furosemide • Heparin • Hydralazine • Hydrochlorothiazide • Labetalol • Lidocaine • Nifedipine • Nitroglycerine • Verapamil
May increase fetal growth restriction	• Angiotensin-converting enzyme inhibitors • Angiotensin receptor blockers • Atenolol • Carvedilol • Metoprolol • Propranolol
May cause β -blockade	• Esmolol
Cyanide toxicity	• Nitroprusside (high doses)
Methemoglobinemia	• Nitroglycerin
Renal malformations	• Angiotensin-converting enzyme inhibitors • Angiotensin receptor blockers
Hemorrhage risk	• Apixaban • Phenytoin • Rivaroxaban • Warfarin
Thyroid toxicity	• Amiodarone
Death	• Angiotensin-converting enzyme inhibitors • Angiotensin receptor blockers
Limited data	• Amlodipine • Procainamide • Flecainide • Clopidogrel

Adapted from American College of Obstetricians and Gynecologists' Presidential Task Force on Pregnancy and Heart Disease and Committee on Practice Bulletins—Obstetrics. ACOG practice bulletin no. 212: pregnancy and heart disease. *Obstet Gynecol.* 2019;133(5):e320–e356. (49)

reducing maternal morbidity. Assuming avoidance of known teratogenic agents, when antihypertensive therapy is indicated, it is generally safe for the fetus. Of the agents listed herein, labetalol is the only one that has been associated with depressed neonatal respiration. (33) There may be an increased risk of fetal growth restriction or having a

small-for-gestational age neonate when β -blockers are used, and the risk is thought to be greatest with atenolol (34); however, it remains unknown whether the medication or the underlying condition leads to the possible fetal growth restriction.

Given the risks of hypertensive disease in pregnancy to the fetus, surveillance with growth ultrasonography and antenatal testing is often recommended to detect fetal growth restriction, oligohydramnios, or other concerns for placental insufficiency. When a pregnant woman with chronic hypertension develops superimposed preeclampsia, maternal morbidity and mortality rates are increased. To mitigate risks of placental insufficiency and superimposed preeclampsia, low-dose aspirin is recommended in pregnancy, starting as early as 12 weeks' gestation. This therapy is advocated by the US Preventive Service Task Force and the American College of Obstetricians and Gynecologists (ACOG) for primary prevention. Based on available data, there does not appear to be an increased risk of placental abruption, hemorrhage, or other adverse maternal or fetal effects. (35) Most hypertensive women can have term deliveries, but they are often planned rather than waiting until labor ensues, as ongoing pregnancy is associated with complications of preeclampsia without clear neonatal benefit.

Many studies have shown that the risks of hypertension in pregnancy extend beyond the peripartum period. A recent retrospective cohort study found that women who experienced a hypertensive disorder of pregnancy were at higher future risk for stroke, coronary artery disease, cardiac arrhythmias, and chronic kidney disease. (36) It is not clear whether the pathophysiologic changes that occur in relation to preeclampsia cause long-term damage that increases the risk for further disease, or whether patients who develop preeclampsia already have an increased baseline risk (due to genetics or other undetected factors) for cardiovascular disease later in life.

Cardiomyopathy

Peripartum cardiomyopathy is a diagnosis of exclusion in women who develop heart failure with a reduced left ventricular ejection fraction less than 45% (8) during the last months of pregnancy or up to 5 months after delivery. The most common etiologies of cardiomyopathy include ischemia, myocarditis, long-standing hypertension, incessant arrhythmias, and stress-mediated cardiomyopathy. The clinical maternal spectrum is quite broad and can range from mild dyspnea and lower extremity edema, to severe hemodynamic instability and cardiogenic shock. Subtle

manifestations may be overlooked because of the presence of similar symptoms in normal pregnancies. There are no specific clinical features that distinguish peripartum cardiomyopathy from heart failure with other etiologies. The pathophysiology of peripartum cardiomyopathy remains uncertain and is likely multifactorial. Symptoms typically develop in the third trimester or in the months following delivery, with a spike in the first month after delivery. (37) Some women are at higher risk of developing peripartum cardiomyopathy, as its incidence is higher in women older than 30 years, African Americans, those with a hypertensive disorder of pregnancy, and those with a multiple gestation pregnancy. (38)

Treatment for this entity depends largely on the severity of dysfunction but can include agents such as β -blockers, hydralazine, diuretics, digoxin, and anticoagulants during pregnancy. In postpartum women, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and spironolactone are also considered for medical therapy. Bromocriptine has been proposed for the treatment of peripartum cardiomyopathy based on preliminary data from small studies demonstrating improved recovery of heart function and reduced mortality. (39) While this therapy may be beneficial, adverse events such as venous and arterial thromboembolism have been associated with this medication; importantly, this drug suppresses lactation. Given the importance of lactation and the fact that the US Food and Drug Administration withdrew this medication for safety concerns, widespread use of bromocriptine has not been advocated in the early postpartum period. The psychosocial effects of a diagnosis of cardiomyopathy are also notable, as several studies have elucidated new depression, sense of doom, and difficulty caring for newborns among mothers who suffered from this disease. (40)(41)

Arrhythmias

Arrhythmias are fairly common in pregnancy and are likely a result of hemodynamic changes, increased sympathetic tone, and increase in myocardial stretch related to the volume load of pregnancy. (42) The true incidence of arrhythmia during pregnancy is unknown, but supraventricular tachycardia is most frequent, with lower incidences of ventricular arrhythmias. (43) Women with a history of arrhythmia before pregnancy are at higher risk for cardiac complications during pregnancy, including recurrent arrhythmia. (16) Increasing maternal age and comorbidities, as well as an increase in the number of pregnant women with congenital heart disease, likely contribute to

this increased risk. The likelihood of recurrent arrhythmias is greater in women with underlying structural cardiac disease. In general, pregnant women should be treated similarly to nonpregnant patients when arrhythmias develop. If the patient has a stable tachyarrhythmia, the management depends on the type of tachyarrhythmia. However, if the woman is unstable with a tachyarrhythmia, immediate direct-current cardioversion is indicated, as maternal stabilization is paramount to fetal stabilization. Guidelines for management of supraventricular tachycardia suggest adenosine as the first-line drug for acute conversion of stable paroxysmal supraventricular tachycardia when vagal maneuvers fail. (22) Preexisting structural heart disease increases the risk of developing atrial fibrillation during pregnancy. In the acute setting for stable women with atrial fibrillation, intravenous β -blockers are recommended for rate control with subsequent transition to oral β -blockers.

Ventricular arrhythmias are much less common than supraventricular arrhythmias during pregnancy. However, premature ventricular beats, which may be asymptomatic or experienced as palpitations, are common in pregnancy. Ventricular tachycardia and/or fibrillation are more typically associated with preexisting structural heart disease and other known causes of ventricular tachyarrhythmias such as long QT syndrome. (44)(45) Like supraventricular tachyarrhythmias, ventricular tachyarrhythmias that present with hemodynamic instability should be treated with immediate cardioversion. For chronic ventricular arrhythmias with or without structural heart disease, β -blockers or non-dihydropyridine calcium channel blockers are often used for prophylaxis. (46)(47)

DELIVERY CONSIDERATIONS

Timing of Delivery

ACOG is clear about the timing of delivery for hypertensive women, advocating for nonsevere hypertensive disease to be delivered at term. (48) However, the timing of delivery in a woman with underlying cardiac disease and the absence of hypertension is not clearly established. At this time, there is no consensus to guide delivery timing for patients with cardiac disease. In the absence of data to guide management, many clinicians advocate for delivery in the setting of worsening cardiac status. However, this practice has not yet been proven to be associated with improved maternal outcomes. Expert opinion suggests that in stable maternal cardiac disease, women can undergo a vaginal delivery at 39 weeks' gestation. (49) Delivery should occur at a hospital with an appropriate level of care, with resources needed to support any

maternal and fetal complications. The location of delivery can be guided by the severity of cardiovascular disease and is addressed by the modified WHO classification system. Ideally, a delivery plan is created with a multidisciplinary care team before any scheduled delivery. If a decision is made to deliver in the preterm period due to decompensation of maternal status, the neonatologist and pregnant patient and family should have informed discussions around the risks of prematurity. At this time, ongoing registry research is attempting to answer the question of what the optimal time for delivery is, so as to balance maternal and fetal risks.

Mode of Delivery

In general, vaginal delivery is preferable to cesarean delivery for women with cardiac disease. The advantages of a vaginal delivery include less blood loss, lower risk of infection, absence of surgical stress, hemodynamic stability, and early ambulation. An important disadvantage is that labor can be prolonged and unpredictable. In addition, the hemodynamic demands of the second stage of labor and delivery may not be tolerated by certain women with specific disease processes. (49) Typically, heart rate, central venous pressure, cardiac output, and systemic arterial pressure all increase during labor. Repeated Valsalva maneuver can result in abrupt reductions in cardiac output and venous return, which may worsen cardiac status in some patients with very high-risk cardiac conditions, particularly those that are preload-dependent. These patients may benefit from regional anesthesia, which can minimize catecholamine release and cardiac output fluctuations. Ideally, a pregnancy cardiac team should determine which patients are not optimal candidates for a vaginal delivery or those who would benefit from an assisted second stage of labor using forceps or vacuum-assisted extraction. Maternal risks of operative vaginal deliveries include larger lacerations, pelvic floor dysfunction, and urinary and fecal incontinence. (50) Fetal risks of operative vaginal delivery include scalp wounds, shoulder dystocia, skull fracture, and intracranial bleeding, but serious neonatal complications are extremely rare.

Cesarean delivery should be reserved for women with severe obstructive lesions, with certain situations involving aortopathies, and those who receive full anticoagulation therapy with warfarin.

IMPLICATIONS FOR THE NEONATE

Congenital Heart Disease—Inheritance

When a pregnant woman has congenital cardiac disease, it is important to consider inheritance of the condition.

Generally, the estimated risk of congenital heart disease for the fetus when the woman has congenital heart disease is approximately 3% to 5%, but ranges from 1% to 15%. (16)(17) In addition, a few autosomal dominant conditions have a higher incidence of recurrence, including DiGeorge syndrome, Marfan syndrome, and hypertrophic obstructive cardiomyopathy. A few other genetic conditions that are commonly associated with congenital heart disease include Noonan syndrome, Down syndrome, Holt-Oram syndrome, and 22q11 microdeletion. Referral for genetic counseling and often fetal echocardiography is recommended.

Fetal Growth Restriction/Fetal Hypoxia

Maternal vascular disease has been implicated as a cause of impaired uteroplacental perfusion and fetal growth restriction. Reduced maternal systolic function, increased systemic vascular resistance, and lack of volume expansion has been correlated with fetal growth restriction to less than the 10th percentile compared to age-matched controls (51) and severe growth restriction to less than the 3rd percentile. (52) Even maternal congenital disease in the setting of normal cardiac output has been associated with fetal growth restriction. (53)(54) In addition, maternal hypertensive disease may contribute to increased placental resistance, which has been correlated with fetal hypoxemia and fetal growth restriction. (55) The pathogenesis of fetal growth restriction in the setting of maternal cardiac disease is thought to be partially related to low umbilical venous oxygen saturation and partial pressure of oxygen values. (33) To compensate for low levels of fetal oxygenation, the fetus will increase the ratio of blood flow to vital organs, specifically the brain and heart, but cardiac output and placental blood flow remain relatively stable. In some acute hypoxic scenarios, the fetus may not be able to adequately perfuse the brain and heart. Based on several cardiac registries, the incidence of small-for-gestational age neonates was approximately 15% to 20% of all cases. Due to the risks of fetal growth restriction, growth ultrasonography in the second and third trimesters is often recommended.

Medications

Safety data on antiarrhythmics in pregnancy is somewhat limited. In some cases, the risk may outweigh the benefit. While β -adrenergic blocking agents are usually well-tolerated in pregnancy and may be indicated for treatment of tachyarrhythmias, severe hypertension, or cardiomyopathy, they have been associated with neonatal respiratory

depression, sustained bradycardia, and hypoglycemia when administered late in pregnancy or just before delivery. (32) Amiodarone has been associated with fetal growth restriction, prematurity, congenital goiter, hypo- or hyperthyroidism, transient bradycardia, and prolonged QT in the newborn. (33) Disopyramide may induce uterine contraction and premature delivery. High serum levels of lidocaine may cause central nervous system depression after birth. Quinidine has been associated with ototoxicity and neonatal thrombocytopenia, and high doses may cause preterm labor or abortion. (33) Data on neonatal toxicity related to other antiarrhythmics, including adenosine, digoxin, flecainide, disopyramide, and procainamide, are limited. However, digoxin, sotalol, and flecainide are used to treat fetal arrhythmias and are thought to be safe in pregnancy. Studies are further exploring the efficacy of these agents in the treatment of fetal arrhythmias, which will provide further safety data once completed. The Table shows more details on medications that are used for cardiovascular disease.

Preterm Birth

The background incidence of preterm birth is approximately 10% in the United States. (1) However, among women with heart disease, this incidence is higher. In large cohorts of women with cardiac disease, the incidence of preterm birth was between 12% and 20%. (16)(17)(18) The increased incidence of preterm birth is thought primarily to be related to iatrogenic preterm delivery from conditions such as preeclampsia, decompensated maternal cardiac disease, or non-reassuring fetal status, though these studies did not distinguish iatrogenic from spontaneous preterm delivery. More data are needed to explore the causes of preterm birth in these pregnancies. Importantly for mothers, preterm birth is associated with psychological distress, including depression, anxiety, and posttraumatic stress disorders. (49) For the newborn, the risks of prematurity vary by gestational age, but are well-established, including but not limited to, the risk of respiratory complications, feeding difficulties, cerebral palsy, developmental delay, and vision and hearing problems. (1)

Fetal and Neonatal Death

In the setting of maternal cardiac disease, the risk for fetal or neonatal loss is increased. In the Cardiac Disease in Pregnancy Study, fetal death occurred in approximately 1% of the cohort; similarly neonatal death complicated approximately 1% of the cohort as well. (16) If a woman

has New York Heart Association functional class II or greater heart failure or cyanosis at baseline, maternal left heart obstruction, tobacco use, multiple gestation, or use of anticoagulants, the fetal/neonatal death rate was doubled. The ZAHARA I and II cohorts (Pregnancy in Women with Congenital Heart Disease Study) noted an intrauterine mortality of approximately 2% to 4%. (17)(18) The exact mechanism of pregnancy loss is poorly understood but may be related to suboptimal placental perfusion as previously mentioned. More data are needed to determine the noted increased risk. Given that there is an increased risk of stillbirth, some experts have proposed antenatal testing, especially in the presence of cyanotic heart disease, but also in the presence of hypertensive disease. In the absence of hypertensive disease, specific protocols are not well defined, nor are the timing and efficacy of antenatal surveillance. (56)

FUTURE DIRECTIONS AND AREAS FOR RESEARCH

Given that many ethical hurdles exist to conducting randomized controlled trials with pregnant women, data on many treatment strategies in pregnancy are often observational or retrospective. Despite the barriers that exist to further research, it is imperative that we continue to collect data to better characterize risk factors, treatment nuances, and outcomes related to pregnancies complicated by cardiovascular disease, especially given that maternal morbidity and mortality associated with cardiac disease continue to rise. Genetic studies to help identify women at risk of developing cardiovascular complications would be helpful for both risk stratification and preconception counseling. In addition, advances in the treatment of preexisting heart disease have led to the survival of many women with congenital malformations or valvular disease to childbearing age, and so the complexity of this patient population will continue to rise.

In particular, given the high prevalence of morbidity associated with preeclampsia and peripartum cardiomyopathy, more research should be dedicated to clarifying the underlying pathophysiology of these disease processes. This will enable the optimization of guideline-directed medical treatment during pregnancy as well as formulate an appropriate longitudinal plan for postnatal care. Clarifying the long-term effects of cardiovascular complications during pregnancy will help with developing more evidence-based guidelines

for screening and treatment beyond the peripartum period. (57)

Finally, given the demonstrated benefit of multidisciplinary cardio-obstetric teams, this model should be adopted not only at large tertiary care centers but also at smaller community sites. Equitable care from a knowledgeable team of providers will be crucial to resolving the stark disparities that unfortunately continue to emerge along the lines of race, socioeconomic class, and access to care.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the physiology of maternal adaptation to pregnancy and know the normal changes in maternal physiologic variables and in laboratory values that occur during pregnancy.
- Know the effects on the fetus and/or newborn infant of maternal cardiac disease and its management.
- Know the effects on the fetus and/or newborn infant of maternal chronic hypertension and its management.
- Know the effects on the fetus and/or newborn infant of mild preeclampsia and its management.

References

- Centers for Disease Control and Prevention. Pregnancy. <https://www.cdc.gov/pregnancy/index.html>. Accessed August 11, 2021
- Hirshberg A, Srinivas SK. Epidemiology of maternal morbidity and mortality. *Semin Perinatol*. 2017;41(6):332–337
- Lima FV, Yang J, Xu J, Stergiopoulos K. National trends and in-hospital outcomes in pregnant women with heart disease in the United States. *Am J Cardiol*. 2017;119(10):1694–1700
- Roos-Hesselink JW, Ruys TPE, Stein JI, et al; ROPAC Investigators. Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. *Eur Heart J*. 2013;34(9):657–665
- Cameron NA, Molsberry R, Pierce JB, et al. Pre-Pregnancy hypertension among women in rural and urban areas of the United States. *J Am Coll Cardiol*. 2020;76(22):2611–2619
- Moaddab A, Dildy GA, Brown HL, et al. Health care disparity and pregnancy-related mortality in the United States, 2005–2014. *Obstet Gynecol*. 2018;131(4):707–712
- Pfaller B, Sathananthan G, Grewal J, et al. Preventing complications in pregnant women with cardiac disease. *J Am Coll Cardiol*. 2020;75(12):1443–1452
- Bauersachs J, König T, van der Meer P, et al. Pathophysiology, diagnosis and management of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Study Group on peripartum cardiomyopathy. *Eur J Heart Fail*. 2019;21(7):827–843
- Davis MB, Walsh MN. Cardio-obstetrics. *Circ Cardiovasc Qual Outcomes*. 2019;12(2):e005417
- Whittaker PG, Macphail S, Lind T. Serial hematologic changes and pregnancy outcome. *Obstet Gynecol*. 1996;88(1):33–39
- Meah VL, Cockcroft JR, Backx K, Shave R, Stöhr EJ. Cardiac output and related haemodynamics during pregnancy: a series of meta-analyses. *Heart*. 2016;102(7):518–526
- Green LJ, Mackillop LH, Salvi D, et al. Gestation-specific vital sign reference ranges in pregnancy. *Obstet Gynecol*. 2020;135(3):653–664
- Elkayam U, ed. *Cardiac Problems in Pregnancy*. 4th ed. New York, NY: Wiley-Blackwell; 2019
- Robson SC, Dunlop W, Boys RJ, Hunter S. Cardiac output during labour. *Br Med J (Clin Res Ed)*. 1987;295(6607):1169–1172
- Canobbio MM, Warnes CA, Aboulhosn J, et al; American Heart Association Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; Council on Functional Genomics and Translational Biology; and Council on Quality of Care and Outcomes Research. Management of pregnancy in patients with complex congenital heart disease: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2017;135(8):e50–e87
- 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(5):515–521
- Drenthen W, Boersma E, Balci A, et al; ZAHARA Investigators. Predictors of pregnancy complications in women with congenital heart disease. *Eur Heart J*. 2010;31(17):2124–2132
- Balci A, Sollié-Szarynska KM, van der Bijl AGL, et al; ZAHARA-II investigators. Prospective validation and assessment of cardiovascular and offspring risk models for pregnant women with congenital heart disease. *Heart*. 2014;100(17):1373–1381
- Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021;143(5):e72–e227
- van Hagen IM, Roos-Hesselink JW, Ruys TPE, et al; ROPAC Investigators and the EURObservational Research Programme (EORP) Team*. Pregnancy in women with a mechanical heart valve: data of the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC). *Circulation*. 2015;132(2):132–142
- Orwat S, Diller G-P, van Hagen IM, et al; ROPAC Investigators. Risk of pregnancy in moderate and severe aortic stenosis: from the multinational ROPAC Registry. *J Am Coll Cardiol*. 2016;68(16):1727–1737
- Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al. 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy. *Kardiol Pol*. 2019;77(3):245–326
- Kamel H, Roman MJ, Pitcher A, Devereux RB. Pregnancy and the risk of aortic dissection or rupture: a cohort-cross-over analysis. *Circulation*. 2016;134(7):527–533
- Cavanzo FJ, Taylor HB. Effect of pregnancy on the human aorta and its relationship to dissecting aneurysms. *Am J Obstet Gynecol*. 1969;105(4):567–568
- Smok DA. Aortopathy in pregnancy. *Semin Perinatol*. 2014;38(5):295–303
- Wanga S, Silversides C, Dore A, de Waard V, Mulder B. Pregnancy and thoracic aortic disease: managing the risks. *Can J Cardiol*. 2016;32(1):78–85
- Silversides CK, Grewal J, Mason J, et al. Pregnancy outcomes in women with heart disease: the CARPREG II Study. *J Am Coll Cardiol*. 2018;71(21):2419–2430
- Gama P, Pancas R, Antunes MJ. Ascending thoracic aorta aneurysm surgery and aortic valve repair during pregnancy. *J Card Surg*. 2009;24(5):547–548
- Hameed AB, Lawton ES, McCain CL, et al. Pregnancy-related cardiovascular deaths in California: beyond peripartum cardiomyopathy. *Am J Obstet Gynecol*. 2015;213(3):379.e1–379.e10
- Azeez O, Kulkarni A, Kuklina EV, Kim SY, Cox S. Hypertension and diabetes in non-pregnant women of reproductive age in the United States. *Prev Chronic Dis*. 2019;16:E146
- Cifu AS, Davis AM. Prevention, detection, evaluation, and management of high blood pressure in adults. *JAMA*. 2017;318(21):2132–2134
- Rey E, Couturier A. The prognosis of pregnancy in women with chronic hypertension. *Am J Obstet Gynecol*. 1994;171(2):410–416
- Resnik R. *Creasy and Resnik's Maternal-Fetal Medicine: Principles and Practice*. 8th ed. Philadelphia, PA: Elsevier; 2018
- Kincaid-Smith P, Bullen M, Mills J. Prolonged use of methyldopa in severe hypertension in pregnancy. *BMJ*. 1966;1(5482):274–276
- United States Preventive Services Taskforce. Screening for gestational diabetes. <https://www.uspreventiveservicestaskforce.org/uspstf/>. Accessed April 27, 2021.
- Garovic VD, White WM, Vaughan L, et al. Incidence and long-term outcomes of hypertensive disorders of pregnancy. *J Am Coll Cardiol*. 2020;75(18):2323–2334. [10.1016/j.jacc.2020.03.028](https://doi.org/10.1016/j.jacc.2020.03.028)
- Elkayam U, Akhter MW, Singh H, et al. Pregnancy-associated cardiomyopathy: clinical characteristics and a comparison between early and late presentation. *Circulation*. 2005;111(16):2050–2055

38. Davis MB, Arany Z, McNamara DM, Goland S, Elkayam U. Peripartum cardiomyopathy: JACC state-of-the-art review. *J Am Coll Cardiol*. 2020;75(2):207–221
39. Kamiya CA, Kitakaze M, Ishibashi-Ueda H, et al. Different characteristics of peripartum cardiomyopathy between patients complicated with and without hypertensive disorders. -Results from the Japanese Nationwide survey of peripartum cardiomyopathy-. *Circ J*. 2011;75(8):1975–1981
40. Park SH, Chin JY, Choi MS, Choi JH, Choi YJ, Jung KT. Extracorporeal membrane oxygenation saved a mother and her son from fulminant peripartum cardiomyopathy. *J Obstet Gynaecol Res*. 2014;40(7):1940–1943
41. Dekker RL, Morton CH, Singleton P, Lyndon A. Women's experiences being diagnosed with peripartum cardiomyopathy: a qualitative study. *J Midwifery Womens Health*. 2016;61(4):467–473
42. Ducas RA, Elliott JE, Melnyk SF, et al. Cardiovascular magnetic resonance in pregnancy: insights from the cardiac hemodynamic imaging and remodeling in pregnancy (CHIRP) study. *J Cardiovasc Magn Reson*. 2014;16:1
43. Vaidya VR, Arora S, Patel N, et al. Burden of arrhythmia in pregnancy. *Circulation*. 2017;135(6):619–621
44. Li J-M, Nguyen C, Joglar JA, Hamdan MH, Page RL. Frequency and outcome of arrhythmias complicating admission during pregnancy: experience from a high-volume and ethnically-diverse obstetric service. *Clin Cardiol*. 2008;31(11):538–541
45. Rashba EJ, Zareba W, Moss AJ, et al; LQTS Investigators. Influence of pregnancy on the risk for cardiac events in patients with hereditary long QT syndrome. *Circulation*. 1998;97(5):451–456
46. Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, et al; European Society of Gynecology (ESG); Association for European Paediatric Cardiology (AEPC); German Society for Gender Medicine (DGesGM); 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(24):3147–3197
47. Priori SG, Blomström-Lundqvist C, Mazzanti A, et al; ESC Scientific Document Group. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J*. 2015;36(41):2793–2867
48. ACOG committee opinion no. 560: medically indicated late-preterm and early-term deliveries. *Obstet Gynecol*. 2013;121(4):908–910
49. American College of Obstetricians and Gynecologists' Presidential Task Force on Pregnancy and Heart Disease and Committee on Practice Bulletins—Obstetrics. ACOG practice bulletin no. 212: pregnancy and heart disease. *Obstet Gynecol*. 2019;133(5):e320–e356
50. Volløyhaug I, Mørkved S, Salvesen KÅ. Authors' reply re: Pelvic organ prolapse and incontinence 15-23 years after first delivery: a cross-sectional study. *BJOG*. 2015;122(12):1715
51. Vasapollo B, Valensise H, Novelli GP, Altomare F, Galante A, Arduini D. Abnormal maternal cardiac function precedes the clinical manifestation of fetal growth restriction. *Ultrasound Obstet Gynecol*. 2004;24(1):23–29
52. Bamfo JE, Kametas NA, Turan O, Khaw A, Nicolaides KH. Maternal cardiac function in fetal growth restriction. *BJOG*. 2006;113(7):784–791
53. Nora JJ, Nora AH. Update on counseling the family with a first-degree relative with a congenital heart defect. *Am J Med Genet*. 1988;29(1):137–142
54. Gelson E, Curry R, Gatzoulis MA, et al. Effect of maternal heart disease on fetal growth. *Obstet Gynecol*. 2011;117(4):886–891
55. Soothill PW, Nicolaides KH, Rodeck CH, Campbell S. Effect of gestational age on fetal and intervillous blood gas and acid-base values in human pregnancy. *Fetal Ther*. 1986;1(4):168–175
56. Grodzinsky A, Florio K, Spertus JA, et al. Maternal Mortality in the United States and the HOPE Registry. *Curr Treat Options Cardiovasc Med*. 2019;21(9):42
57. Countouris ME, Villanueva FS, Berlacher KL, Cavalcante JL, Parks WT, Catov JM. Association of hypertensive disorders of pregnancy with left ventricular remodeling later in life. *J Am Coll Cardiol*. 2021;77(8):1057–1068