Pregnancy in Women with Cardiovascular Diseases

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ABSTRACT: Patients with cardiovascular disease represent a significant cohort at risk for complications during pregnancy. The normal physiologic changes of pregnancy could further compromise the hemodynamics of various cardiovascular conditions, resulting in clinical deterioration and even death. The fetus of a gravida with cardiovascular disease also has an increased risk of morbidity, including an increased risk of inherited cardiac genetic disorders, fetal growth restriction, and premature delivery. These complications also increase the risk for antenatal and perinatal mortality. Ideally, the management of a patient with cardiac disease who is considering pregnancy should start with pre-conception counseling that outlines the maternal and fetal complications associated with her particular cardiac disorder. The pregnancy is best managed by a dedicated team of specialists in maternal-fetal medicine, cardiology, cardiovascular surgery, anesthesiology, and neonatology, preferably in a tertiary care center.

INTRODUCTION

The population demographics of pregnant women have been changing in the past 20 years, bringing about an increase in the number of pregnant patients with cardiovascular diseases. Several factors are contributing to these changes. The most prevalent is the shift of childbearing years from a woman's early 20s to her 30s and 40s, resulting in an increased number of pregnant patients with chronic hypertension and coronary artery disease.[1,2] Perimenopausal woman undergoing in vitro fertilization represent a separate at-risk group for cardiovascular disease in pregnancy.[2] There has also been an increase in the number of pregnancies in patients with congenital heart disease that was either repaired in childhood or is still being monitored.[3] The pregnant patient with cardiovascular disease faces significant risks, both to her health and the health of the offspring, including an increased risk for exacerbation of primary disease, acute cardiovascular decompensation, premature delivery, and death.[4-6] Certain conditions put patients at especially high risk for both maternal and fetal complications, including pulmonary vascular disease, maternal cyanosis, poor maternal functional class, arrhythmias, and the need for anticoagulants.[7-11]

Management of pregnant patients with cardiovascular disease requires a dedicated team of physicians, including a cardiologist, cardiovascular surgeon, maternal-fetal medicine specialist, and neonatologist who will strive to reach the optimal pregnancy outcome. For patients with severe cardiovascular risks, delivery in a tertiary care center capable of multispecialty coordinated obstetrical/cardiovascular care is advised.

In this review, we address the physiological changes of pregnancy and management of some of the more common cardiac diseases in a parturient, including hypertensive disease in pregnancy, congenital valvular diseases, cardiomyopathy, and diseases of the aorta.

PHYSIOLOGIC CHANGES IN PREGNANCY

Pregnancy is associated with major physiologic adaptions that are necessary to ensure adequate blood flow to the uterus to support the growth of the fetus.[12,13] During the first trimester, there is an upregulation of the renin-angiotensin-aldosterone system that increases the retention of sodium and water.[12,13] Simultaneously, hormonally mediated stimulation of the liver and bone marrow leads to increases in protein synthesis and hematopoiesis, respectively. This results in a gradual increase in red cell mass of between 50% and 60% above pre-pregnancy values at the end of the second trimester[12]; furthermore, plasma volume increases by between 30% and 50% prior to 30-weeks' gestation. Peripheral vascular resistance starts falling during the first trimester, due in part to uteroplacental shunting and to the decrease in vascular responsiveness to the pressor effect of angiotensin II[14] and norepinephrine.[8] Maternal heart rate increases by 10 to 15 beats per minute.[15] The increase in preload, decrease in afterload, and increased heart rate lead to an increase in cardiac output (Table 1).[16-19]

PRENATAL CARE

A patient with congenital heart disease, valvular disease, arrhythmia, cardiomyopathy, or other types of cardiac disease is at risk for developing congestive heart failure, pulmonary edema, and uncontrolled arrhythmias. In addition, aortic disease increases the risk of aortic dissection or rupture of an aneurysm. There are several periods of pregnancy in which the patient is at increased vulnerability for complications: the end of the first trimester, the second trimester at approximately 20 weeks gestational age, and at 29 to 30 weeks gestational age, when

PHYSIOLOGIC PARAMETER	CHANGE
Heart rate	Increased 15-20 bpm
Cardiac output	Increased 30-50%
Blood pressure	Decreased by 10 mm Hg
Peripheral vascular resistance	Decreased
Blood volume	Increased 30-50%
Red cell mass	Increased 20-30%

Table 1.
Physiologic changes in pregnancy.

the blood volume increase is maximal.[12,13] The most critical time for the parturient with cardiovascular disease, however, is peripartum. During labor, the increase in catecholamines leads to a marked increase in maternal heart rate and cardiac output. Each uterine contraction autotransfuses up to 500 mL of blood from the uterus into the maternal vascular system, significantly increasing the preload. This autotransfusion persists immediately after delivery. There are also major shifts of fluids from the extravascular to the intravascular maternal compartment during the immediate postpartum period. Thus, the patient with cardiac disease is at an increased risk for cardiac failure, especially in the peripartum period.

Managing the fetus in a gravida with heart disease can be more challenging given the increased risk of fetal complications. For example, the fetal risk of inheriting congenital heart disease is from 2% to 3% in simple valvular disease, from 3% to 6% in complex congenital heart disease, and up to 50% in autosomal dominant syndromes such as Noonan's or Marfan's.[5,20,21] The fetus is also affected by poor placentation that can stem from a decrease in uterine perfusion secondary to decreased cardiac output, which can lead to an increased risk for fetal growth restriction, oligohydramnios, and possibility intrauterine fetal demise. Finally, the fetus is at risk for complications of prematurity regardless of whether premature delivery was indicated for maternal or fetal complications. Antenatal fetal surveillance includes ultrasound evaluation of fetal anatomy and monitoring of fetal growth, amniotic fluid volume, and placental function.

Prenatal care of all patients should start before conception. This holds especially true for patients with cardiovascular disease.[22] In preparation for pregnancy, the cardiac patient needs comprehensive laboratory work and a detailed cardiovascular workup including an ECG, echocardiogram, basic metabolic profile, complete blood count, and further testing as needed (i.e., potential stress testing, cardiac MRI). However, close attention is essential as some testing modalities involve radiation and therefore are contraindicated during pregnancy. The goal is to optimize the patient's cardiovascular status. In addition to a thorough cardiologic evaluation, the patient should have pre-conception maternal-fetal medicine and possibly genetics consultations. These consults provide the patient with realistic expectations of potential complications,[22,23] the opportunity to reflect on her choice of becoming pregnant, and the option of exploring another mode of parenting or reproduction, such as adoption or surrogate pregnancy.

MANAGEMENT OF SPECIFIC CARDIOVASCULAR DISEASES IN PREGNANCY

Chronic Hypertension

Chronic hypertension is the most frequent cardiovascular disorder encountered in pregnancy. Patients are advised to consider pregnancy only if their blood pressure is in good control using antihypertensive agents that are not associated with embryopathy and that are safe to continue during pregnancy. The American College of Obstetricians and Gynecologists (ACOG) advises that mild hypertension may be untreated in pregnancy if blood pressure can remain de novo at 140/90 mm Hg. Most physicians will treat blood pressures above 150/100 mm Hg with antihypertensive agents. Severe hypertension is associated with lower birth weight, preeclampsia, and HELLP (hypertension, elevated liver function, low platelets) syndrome. Women with chronic hypertension who are not under tight control have a higher rate of severe maternal morbidity.

It is reasonable to initiate rest as an initial treatment modality. Methyldopa and hydralazine have the longest track record for managing hypertension in pregnancy but are often associated with side effects that lead to noncompliance.[24-26] Beta blockers and calcium channel blocking agents are administered with relative safety and efficacy.[27-30] Labetalol and nifedipine are most frequently used, although metoprolol is also an acceptable agent.[31] Diuretic agents can contribute to a decrease in placental perfusion and are reserved for patients at risk for congestive heart failure.[32] Patients whose chronic hypertension is well controlled with antihypertensive agents at the start of pregnancy will often experience lower blood pressure at 12 to 14 weeks gestation, when peripheral vascular resistance drops; this is followed by a gradual rise in blood pressure, which necessitates an increased dosage of the antihypertensive agent.[33] Patients with chronic hypertension have a significantly

Class I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Table 2.
New York Heart Association (NYHA) Functional Classifications.[37]

increased risk for developing superimposed preeclampsia that is treated with rest if mild or requires delivery if severe. The recently published ASPRE study shows that low-dose aspirin may decrease the severity and delay the onset of preeclampsia in high-risk patients.[34] Patients with hypertension and end-organ disease such as hypertensive cardiac hypertrophy, cardiomyopathy, pulmonary hypertension, or renal disease are at a significant risk for severe morbidity and potentially death. Their fetuses are at risk for intrauterine growth restriction, premature delivery, and fetal demise.[35]

Cardiac Valvular Disease

Maternal cardiac valvular disease presents another subgroup of diseases that require close multidisciplinary care during pregnancy. The incidence of rheumatic heart disease has fallen drastically in the United States. The majority of cardiac valve disease in pregnancy is secondary to congenital valve disease, either monitored or repaired. Mitral and aortic valve stenosis in the mild form, classified as New York Heart Association Class 1 or 2, are well tolerated in pregnancy (Table 2).[36,37] Patients with mitral stenosis are at an increased risk for atrial fibrillation and pulmonary edema. Standard treatment includes administration of beta blockers to control maternal heart rate and increase diastolic filling time and anticoagulants to decrease the risk of atrial embolism. The most vulnerable period for patients with aortic stenosis is at the time of delivery, regardless of the gestational age at that time. It is important to keep the maternal heart rate at 90 beats per minute or less to allow for adequate filling time of the left ventricle. Maternal tachycardia can lead to a rapid decline in cardiac output. The preload must be maintained adequately, especially when placing regional anesthesia, since decline in preload can also cause a decrease in cardiac output. The balance of fluids peripartum is precarious; an increase in preload can lead to an increase in pulmonary edema.

As with mitral stenosis, aortic stenosis in the mild form is manageable with beta blockers and rest. The most dangerous time for patients with aortic stenosis is at the time of delivery, regardless of the gestational age at that time. Patients with aortic stenosis are dependent on high preload, and any factor that contributes to a decrease in venous return can lead to an acute decrease in cardiac output. Epidural analgesia must be carefully titrated after adequate prehydration, and aggressive management of postpartum bleeding must be instituted.

Patients with severe (< 1.5 cm^2 area) mitral stenosis or severe (< 1 cm^2 area) aortic stenosis are at a significant risk for cardiac decompensation in pregnancy and should consider termination.[10,38] If a patient continues the pregnancy, her hemodynamic status should be monitored frequently in the hospital until reasonable viability is reached and preterm delivery is advised. For a patient who has cardiac decompensation prior to viability, percutaneous valvuloplasty or valvular repair is indicated.

Mitral insufficiency is usually well tolerated in pregnancy, although patients are at an increased risk for arrhythmia. Aortic insufficiency is also well tolerated in the milder forms with NYHA Class 1 and 2 patients. Even severe aortic insufficiency is well tolerated if left ventricular function is normal.[9,38] In a patient with severe aortic regurgitation and left ventricular systolic dysfunction, left ventricular dilation, or pulmonary hypertension, the risk of congestive heart failure is very high.[39] Pharmacological treatment consists of beta blockers, vasodilators (nifedipine), diuretics, and rest, whereas angiotensin-converting enzyme inhibitors are contraindicated in pregnancy.

Pulmonary stenosis is well tolerated if normal right ventricular function is present.[40] In the presence of right heart failure, a complex pharmacologic regime together with maternal rest is indicated. Similarly, pulmonary regurgitation is well tolerated in

pregnancy unless right-sided heart failure is present.[41] Pulmonary valve disease is generally seen most often in patients with repaired tetralogy of Fallot (Table 3). Tricuspid valve disease is uncommon but usually well tolerated in pregnancy.

Patients who have a valvular prosthesis require very intense antepartum and intrapartum management. Antibiotic prophylaxis in labor is recommended to prevent subacute bacterial endocarditis. Anticoagulation is not required in hemodynamically stable patients with bioprosthetic valves, but patients with mechanical valves are at an increased risk for thromboembolism and therefore require anticoagulation. Coumadin (warfarin) is the anticoagulant of choice; unfortunately, it can be associated with embryopathy in the first trimester and should not be used peripartum due to the risk of bleeding. The risk of embryopathy is dose dependent, however, and may be negligible if a 5-mg dose of warfarin daily achieves an adequate level of anticoagulation in the patient. Thus, a patient who takes a maximum 5-mg dose of Coumadin daily may consider taking it in the first trimester after discussing the benefits and risks with her physician.[42-44]

Unfractionated and low-molecular-weight (LMW) heparin are reported to be associated with an increased risk for thrombosis compared to warfarin.[45] Literature suggests, however, that this increased rate of thrombosis may be due to subtherapeutic dosing or patients' lack of compliance.[45-47] A therapeutic dose of LMW heparin achieving a target anti-Xa range of 0.8 to 1.2 U/mL at 4 to 6 hours after administration—given in two divided doses 12 hours apart—can achieve acceptable anticoagulation.[47,48] It is difficult to achieve a therapeutic dose of unfractionated heparin administered subcutaneously and technically difficult to have continuous intravenous heparin during pregnancy. Unfractionated heparin also can interfere with calcium deposit in bones, leading to osteoporosis with long-term use; therefore, use of LMW heparin is preferable to unfractionated heparin for the duration of the pregnancy.

Although Coumadin can be taken safely at a maximal dose of 5 mg/day throughout pregnancy (adjusting the dose to achieve a therapeutic international normalized ratio), there are other anticoagulation options for pregnant women with a mechanical valve. A conservative approach would be to use LMW heparin in the first trimester, then change to warfarin through the second and third trimesters followed by peripartum bridge therapy with LMW intravenous heparin. Patients who prefer no fetal warfarin exposure can use LMW heparin from conception until the peripartum period. Low-dose aspirin administration in conjunction with warfarin or LMW heparin is also

CARDIOVASCULAR CONDITION	POTENTIAL COMPLICATIONS
Chronic hypertension	Preeclampsia HELLP syndrome
Mitral stenosis	Tachycardia-associated decrease in cardiac output Pulmonary edema
Mitral regurgitation	Increased risk of arrhythmia Increased risk of pulmonary edema
Aortic stenosis	Decreased cardiac output with decreased preload
Aortic regurgitation	Generally well tolerated Congestive heart failure
Pulmonary stenosis	Generally well tolerated Pulmonary edema if right-sided heart failure present
Pulmonary regurgitation	Generally well tolerated Pulmonary edema if right-sided heart failure
Tricuspid stenosis	Well tolerated
Tricuspid regurgitation	Well tolerated
Cardiomyopathy	Arrhythmia Congestive heart failure Pulmonary edema
Aortic aneurism	Dissection of aorta, rupture

Table 3.
Major potential complications in pregnancy by cardiovascular diagnosis. HELLP: hemolysis, elevated liver enzymes, low platelet count.

recommended from the second trimester until 10 days prior to planned delivery.[23] The 2014 American Heart Association/ American College of Cardiology guidelines support this approach.[23]

Cardiomyopathy

Cardiomyopathy in a pregnant patient is most frequently acquired from a previous viral infection or exposure to cardiotoxic drugs (cocaine, Adriamycin), or it may be secondary to previous myocardial infarction or previous peripartum cardiomyopathy. The stress of physiologic changes that lead to increased cardiac output during pregnancy can also lead to decompensation of cardiac function. There is, however, insufficient data to provide patients with their risk of decompensation during pregnancy. The general consensus is that patients with a left ventricular ejection fraction less than 45% or NYHA Class 3 or 4 are at increased risk for worsening of the disease and should be advised to avoid pregnancy. Management of these patients during pregnancy requires a complex regime that includes restricting activity, diuretics, digoxin, vasodilators, and early controlled delivery. Anticoagulation in pregnancy is recommended with either a LMW heparin or warfarin, following the 2014 American Heart Association guidelines.[23] Peripartum patients on full anticoagulation are managed with bridge heparin therapy. Hypertrophic cardiomyopathy is usually well tolerated in pregnancy,[49-51] but monitoring for arrhythmias and early signs of congestive heart failure is essential in achieving an optimal outcome. In these cases, a decrease in physical activity becomes an essential part of the treatment regime.

Aortic Aneurysm

Patients with aortic disease represent a particularly at-risk group for sudden death due to pregnancy. The most frequent etiology of aortic aneurysm in a pregnant patient is Marfan syndrome, although other diseases involving the collagen matrix may also predispose a patient to developing an aortic aneurysm.

A patient with aortic dilation of less than 4 cm has a relatively low risk of aortic aneurysm dissection or rupture. There is a consensus of the American College of Cardiologists that dilation of greater than 4.5 cm should be repaired prior to pregnancy or in the immediate postpartum period.[52] A patient with aortic dilatation of 4.5 cm or greater has a significantly increased risk of aortic dissection or rupture during her puerperium,[53] and she should be monitored postpartum in a setting capable of immediate aortic root surgery. The pregnancy should be monitored closely for signs of cardiac dysfunction, as this frequently requires a decrease in maternal activity and close monitoring in a hospital setting if she becomes symptomatic prior to term. Controlling maternal heart rate with beta blockers is the mainstay of therapy. Delivery is orchestrated under controlled circumstances with the assistance of obstetric, cardiac, cardiovascular, anesthesia, and neonatal specialists.[54] Although vaginal delivery is possible under controlled circumstances, most patients will deliver by controlled cesarean section.

CONCLUSION

By understanding the physiologic cardiovascular changes in pregnancy and the specific challenges of different cardiac disease processes, physicians can tailor the patient's care to optimize monitoring of her pregnancy and prepare for the anticipated time and mode of delivery. This understanding also gives us the opportunity to transfer care of those who are at significant risk for cardiac compromise to a center that has the resources to provide critical cardiac care, cardiovascular surgery, and neonatal care.

KEY POINTS:

- During pregnancy, there is a physiological increase in blood volume, heart rate, and cardiac output.
- Patients with an underlying cardiac disorder do not tolerate these changes well and are at risk for developing arrhythmias, pulmonary edema, and congestive heart failure.
- Patients with hypertensive disorders are also at risk for developing preeclampsia and HELLP (hypertension, elevated liver function test, and low platelet count) syndrome.
- Maternal cardiac dysfunction can lead to altered uterine perfusion, resulting in fetal growth abnormalities and necessitating premature delivery.
- Managing a pregnant patient with cardiovascular disease requires a multidisciplinary team approach involving maternal-fetal medicine, cardiology, cardiovascular surgery, anesthesiology, and neonatology specialists, preferably at a tertiary care center.

Conflict of Interest Disclosure:
The author has completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement and none were reported.

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