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Pregnancy and Cardiovascular Disease (N Scott, Section Editor)

Update on Valvular Heart Disease in Pregnancy

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Opinion statement

Valvular heart disease in women of childbearing age poses an increased risk of adverse maternal and fetal outcomes, and management in pregnancy can be challenging. Ideally, patients with suspected valvular disease should have preconception counseling by a multidisciplinary team including cardiologists with expertise in pregnancy and a maternal-fetal medicine specialist. Preconception planning should include a cardiac assessment of maternal risk, determination of frequency of surveillance, and a cardiovascular management plan during delivery. Women with valvular heart disease should be followed closely by a cardiologist and monitored for signs and symptoms of congestive heart failure and arrhythmias. In general, stenotic lesions may become more symptomatic in pregnancy, whereas regurgitant lesions are generally well tolerated. Left-sided valvular lesions have higher complication rates than right-sided lesions. For patients with asymptomatic valvular stenosis, medical management during pregnancy may include beta blockade and/or diuretics. Exercise stress testing prior to pregnancy in sedentary patients can be helpful to unmask symptoms and determine functional capacity. Patients with symptomatic, severe left-sided valvular obstruction have a high maternal risk of cardiovascular events during pregnancy, and percutaneous balloon valvuloplasty or surgery is recommended prior to pregnancy. The type of prosthetic valve (mechanical vs bioprosthetic) should be selected after a careful discussion with the patient. Invasive procedures are generally reserved for when medical management fails. The second trimester may be the optimal time for intervention as fetal organogenesis is complete and the cardiac positioning has not been affected by the gravid uterus.

Introduction

Hemodynamic changes of pregnancy

An understanding of the hemodynamic changes of pregnancy is important in order to predict the effects of pregnancy on women with valvular disease. Pregnancy causes a physiological increase in heart rate, plasma volume, and red blood cell mass. The increase of red blood cell mass is less than the increase in plasma volume, leading to an overall physiological anemia of pregnancy. Increased endothelial prostacyclin and the placental vasculature lead to systemic vasodilation and a decrease in systemic vascular resistance. The increase in preload and the decrease in afterload lead an increase in stroke volume. Cardiac output increases by 30–50% with pregnancy, usually plateaus at around 16 weeks, and then falls after delivery. Patient position affects cardiac output due to compression on the inferior vena cava by the gravid uterus and the effects are most marked near term (38–40 weeks gestation) [1]. Thus, late in pregnancy, the cardiac output is the highest in the left lateral decubitus position. Overall, there is no change in the left ventricular ejection fraction with pregnancy.

The hemodynamic changes associated with pregnancy are more pronounced during labor and are still present after delivery. Labor leads to a further increase of cardiac output due to pain (increasing heart rate) and contractions (increasing stroke volume related to an "auto-transfusion" of blood from the uterus). After delivery, the contracted uterus decompresses the inferior vena cava allowing for increased venous return to the heart. This increased preload increases cardiac output initially; however, cardiac output will decrease to prelabor values within hours after delivery and continue to fall towards baseline over the following 6 months [2••]. Patients with valvular heart disease should be monitored closely during labor and after delivery for clinical signs and symptoms of heart failure as intervention may be required.

Maternal risk assessment

Maternal risk assessment is critical to appropriately provide preconception counseling and treat women during pregnancy. Maternal mortality in those with a history of valvular heart disease can be as high as 2%, 100-fold higher than a normal healthy counterpart. The ROPAC registry was established by the European Society of Cardiology and included patients from both developing and developed countries. Of the 1321 pregnancies evaluated between 2007 and 2011, 334 of pregnancies were in women with valvular disease and 13 died. Of note, four of the seven deaths that occurred in developing countries were in women with mitral stenosis [3]. Generalization of the ROPAC registry data to the developed world and to tertiary care centers in particular should be done with caution, as risk estimates based on this registry are probably high. The World Health Organization (WHO) classifies maternal risk with pregnancy based on preexisting valvular lesions [4]. In that classification system, women with WHO Class I have low maternal cardiovascular risk with pregnancy, whereas those in WHO Class IV have prohibitive risk.

Trials such as CARPREG [5] and ZAHARA [6] also evaluated maternal risk and developed risk assessment scores. CARPREG prospectively evaluated 546 women during pregnancy with primary diagnoses of congenital heart disease (74%), acquired cardiac lesions (22%), or symptomatic arrhythmias (4%). Approximately 18% of the patients had either mitral stenosis or valvular aortic stenosis of varying severity. A CARPREG risk factor score was developed which includes maternal functional status (NYHA class) or cyanosis, left ventricular function, left heart obstruction (mitral valve area <2 cm^2, aortic valve area <1.5 cm^2), and history of prior cardiac events (arrhythmia, stroke, or heart

failure). However, patients with moderate aortic stenosis (valve area 1.0 to 1.4 cm^2) are more likely to tolerate the hemodynamic changes of pregnancy than those with severe aortic stenosis, and the CARPREG score may overestimate risk in these individuals.

ZAHARA [6] followed women with congenital heart disease during pregnancy and identified risk factors for adverse cardiac complications. These risk factors include a history of arrhythmias, NYHA functional class III/IV, left heart obstruction, presence of mechanical valve prosthesis, moderate/severe systemic or pulmonic aorto-ventricular valve regurgitation, the use of cardiac medication prior to pregnancy, and cyanotic heart disease.

General management principals

Individuals with valvular heart disease are usually followed during pregnancy by a cardiologist with experience in the hemodynamic shifts associated with pregnancy. The increase in stroke volume and heart rate is poorly tolerated by women with mitral stenosis, as these changes lead to increased valvular gradients and elevated left atrial and pulmonary pressures. Similarly, women with significant aortic stenosis may have thickened and noncompliant left ventricles that cannot tolerate the increased plasma volume of pregnancy (especially in the setting of a fixed, reduced aortic valve orifice area), and heart failure may occur. Regurgitant lesions are usually tolerated in pregnancy due to the placenta-related decrease in systemic vascular resistance (decreased afterload) that offsets the detrimental effects of increased plasma volume (increased preload) (Fig. 1).

Clinical assessment of filling pressures (e.g., JVP, lung sounds, peripheral edema) is monitored, and medical management with beta blockers and/or diuretics is prescribed if needed. Baseline echocardiogram is usually ordered to assess overall cardiac function and baseline valvular function. A repeat echocardiogram is usually ordered at around 28–32 weeks, during maximal hemodynamic load conditions, to reevaluate valve function.

For those at the highest maternal risk for cardiovascular complication, such as those with severe mitral stenosis, monitoring during labor and delivery in the intensive care unit may be necessary. These patients are also usually seen on consultation by cardiac anesthesia and a delivery plan is formulated. Invasive monitoring with an arterial pressure line may be helpful in patients where sudden blood pressure changes may have significant hemodynamic consequences. Central venous monitoring may be considered in those in which a sudden increase in right atrial pressure may need to be acted on quickly such as those with cardiomyopathy. Judgment on which patients should be monitored in the intensive care unit depends on the experience and comfort level of the managing team.

Postpartum hemodynamic shifts associated with blood loss and placenta venous return can be deleterious in the first few days postpartum and is the period for the highest risk of congestive heart failure and arrhythmia. Specifically, patients with regurgitant lesions may need diuresis or afterload reducers during this period.

Right-sided heart valvular lesions are usually well tolerated in pregnancy, so this review will focus on individual left-sided valvular lesions and the management during pregnancy.

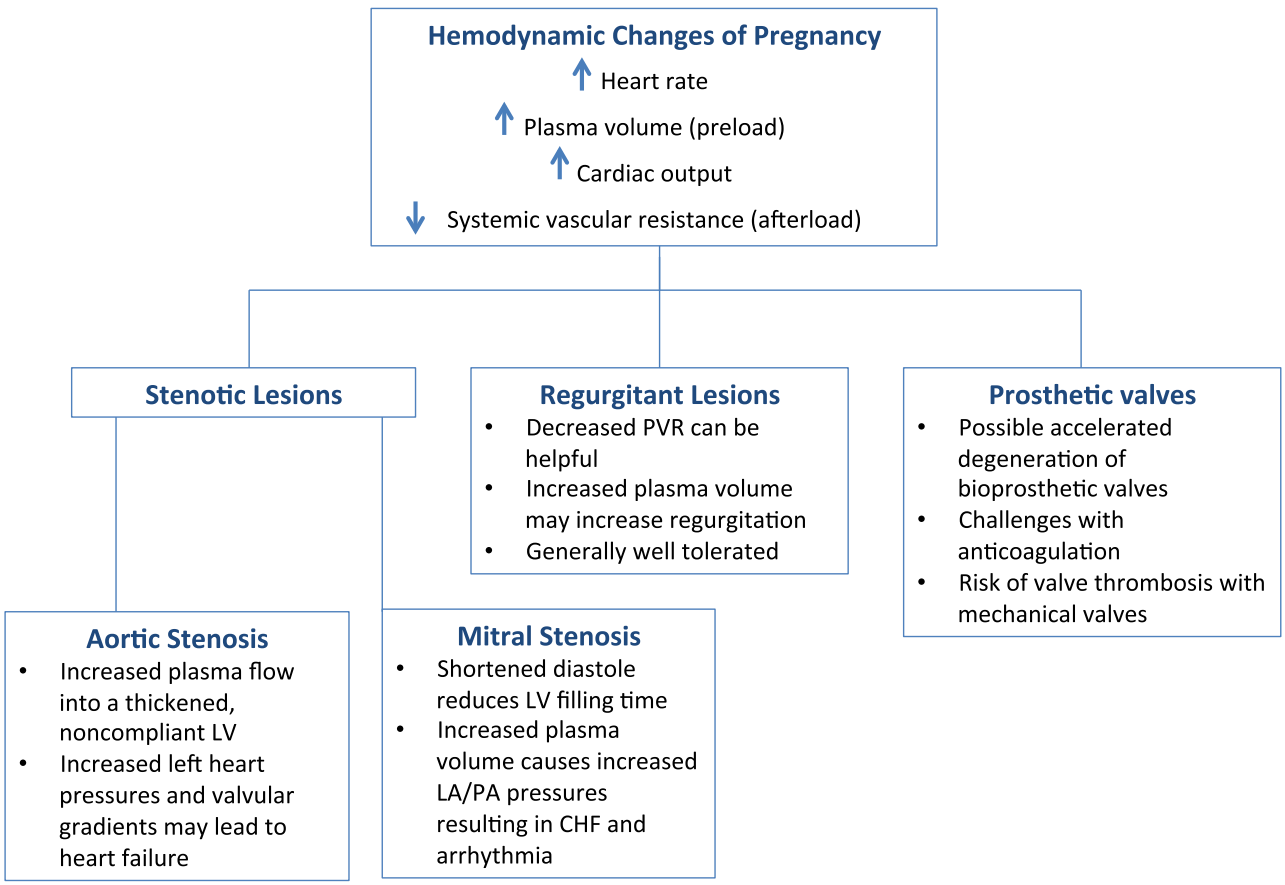

Fig. 1. Flow chart showing the general concepts of valvular heart disease in pregnancy. *CHF* congestive heart failure, *LA* left atrium, *LV* left ventricle, *PA* pulmonary artery.

Aortic valve

Aortic stenosis

Aortic stenosis in the pregnant population is almost always either congenital (e.g., bicuspid aortic valve) or acquired (e.g., rheumatic heart disease). Maternal risk of pregnancy with aortic stenosis is associated with the presence of symptoms and severity of stenosis. Most patients with mild or moderate aortic stenosis are able to tolerate pregnancy without adverse cardiovascular events; however, patients with symptomatic, severe aortic stenosis are at increased risk of events with pregnancy. Severe aortic stenosis is defined as an aortic valve area of <1.0 cm^2, a peak velocity gradient of >4 m/s, and a mean velocity gradient of >40 mmHg by Doppler echocardiography [7••]. A baseline echocardiogram is important, as aortic valve gradients are expected to increase with the increased

cardiac output seen with pregnancy, but the valve area will usually remain stable due to the slowly progressive nature of this lesion (Table 1).

Exercise stress testing may be beneficial in those with severe asymptomatic disease to evaluate functional capacity prior to pregnancy, development of symptoms with exertion, and to monitor for exercise induced drop in blood pressure, which portends an adverse prognosis. If pregnancy does occur in those with asymptomatic severe aortic stenosis, frequent follow-up with a careful assessment of symptoms and clinical exam is recommended. A repeat echocardiogram should be considered for any changes in symptoms or physical exam and at some point in the mid-late second trimester when cardiac output has peaked. Individuals with *symptomatic* severe aortic stenosis (WHO class IV) are considered extremely high risk and pregnancy is contraindicated.

Aortic stenosis may lead to left ventricular hypertrophy, diastolic dysfunction, or left ventricular systolic dysfunction. In those with significant stenosis, the decreased aortic valve orifice area makes it difficult to augment the stroke volume as is required during pregnancy. Also, increased plasma volume into a noncompliant left ventricle may lead to increased left heart pressures and ultimately heart failure. Management of these patients is focused on careful volume assessment and blood pressure management.

Medical management with beta blockade and/or diuretics may be recommended in those individuals who begin to show signs or symptoms of heart failure with pregnancy to increase diastolic filling time and minimize decrease filling pressures, being mindful that these patients are also preload dependent.

Table 1. Simplified cardiology management for specific valvular lesions

Valve lesion	Maternal risk	Cardiology follow-up	Management/treatment
PS, MVP	Very low	1–2 visits	Expectant management
Repaired tetralogy of Fallot	Low-moderate	Per trimester	Expectant management, diuretics, holter monitor, and beta blockers as needed for arrhythmia
Asymptomatic regurgitant lesions	Low or moderate	Per trimester	Expectant management, diuretics
Mild-moderate stenosis	Low-moderate	Per trimester	Beta blockers and diuretics as needed
BAV with aorta <45 mm	Moderate	Variable	Blood pressure and heart rate control. Echocardiography to follow aortic size in pregnancy
Mechanical valves	High	Monthly or bimonthly	Warfarin in second and third trimester only or LMWH throughout with anti-Xa leverls
BAV with aorta 45–50 mm	High	Monthly or bimonthly	Consider aortic repair prior to pregnancy. Blood pressure and heart rate control. Consider C-section
Severe symptomatic MS or AS	Prohibitive		Valvuloplasty or surgery prior to pregnancy
BAV with aorta >50 mm	Prohibitive		Aortic repair prior to pregnancy

Displays valvular heart disease examples and recommendations on cardiology follow-up and management. *Ao* aorta, *AS* aortic stenosis, *BAV* bicuspid aortic valve, *C-section* cesarean section, *PS* pulmonary stenosis, *MS* mitral stenosis, *MVP* mitral valve prolapse

For those who are unresponsive to medical management, percutaneous valvuloplasty may be required. Cesarean section followed by surgical valve replacement in those whose valvular morphology does not permit valvuloplasty may be necessary. A maternal mortality rate of 17% and fetal mortality rate of 32% for those women who undergo valvular surgery while pregnant have been reported [7••].

Bicuspid aortic valve (BAV) is the most common congenital heart abnormality and is associated with dilation of the aortic root and ascending aorta [8]. The ascending aorta often cannot be completely imaged by echocardiography, and computed tomography (CT) or magnetic resonance imaging (MRI) may be needed to fully evaluate for aortic dilation. Women with a BAV and aortic diameters of 45–50 mm are WHO class III and have an increased risk of aortic dissection during pregnancy. Surgery is recommended prior to pregnancy if the ascending aorta diameter is greater than 50-mm preconception [9•].

Cesarean section is generally reserved for obstetric indications; however, there are a few cardiac indications in which it can be considered, such as intractable heart failure or a dilated aorta (> 45 mm). If vaginal delivery is chosen, minimizing the hemodynamic effects of Valsalva using a facilitated second stage of labor (forceps or vacuum extraction) may be performed. Also, placing the patient in the lateral decubitus position will increase the cardiac output. Routine antibiotic prophylaxis for severe aortic stenosis during labor is generally not required though careful attention should be paid to unexplained fevers [10, 11].

Aortic regurgitation

Aortic regurgitation during pregnancy is usually well tolerated as the hemodynamic changes of pregnancy are favorable, mostly due to the decrease in systemic vascular resistance and decreased time diastolic time secondary to increases in heart rate. Patients with severe regurgitation should undergo preconception evaluation. Preconception surgery is indicated for symptomatic patients with severe aortic regurgitation or those who meet the ACC/AHA guidelines for intervention, e.g., left ventricular ejection fraction of <50% [7••]. Asymptomatic patients with severe aortic insufficiency may be evaluated with an exercise stress test to confirm the absence of symptoms. Chronic severe aortic regurgitation in the setting of left ventricular dysfunction or acute onset severe aortic regurgitation is usually not well tolerated with pregnancy and is at risk for development of heart failure [12]. Diuresis (such as with loop diuretics) or an afterload reducers (such as nifedipine or labetalol) may be needed during labor and/or in the immediate postpartum period to help control volume status [13].

Mitral valve

Mitral stenosis

Mitral stenosis can be congenital, but in women of childbearing age, it is most often a sequela of rheumatic heart disease. Severe mitral stenosis is defined as a mitral valve area of <1.5 cm^2 and a diastolic pressure half time of ≥150 ms. Due to the variability seen with heart rate, mean Doppler pressure gradients are no longer recommended to classify patients and have been removed from the most recent ACC/AHA guidelines [7••]. The WHO classifies those with severe mitral

stenosis as class IV, prohibitive maternal cardiovascular risk with pregnancy.

The hemodynamic effects of pregnancy (specifically the increased plasma blood volume and increased heart rate) can lead to increased transmitral valve gradients, increased left atrial pressure, and increased pulmonary venous pressure and pulmonary edema. Patients with mitral stenosis are also at higher risk for atrial arrhythmias [14].

Symptoms of mitral stenosis can be managed using beta blockers or diuretics. Beta blockers decrease the heart rate and thus lengthen the diastolic filling time and decrease transvalvular gradients. As the heart rate physiologically increases with pregnancy, titration of beta blockers as pregnancy progresses may be required. Diuretics reduce left atrial pressure; however, they should be used cautiously to avoid placental hypoperfusion. The hypercoaguability-associated pregnancy increases the risk for thrombus formation, and for those with atrial fibrillation, anticoagulation should be continued during pregnancy.

Percutaneous balloon commissurotomy may be performed to treat severe mitral stenosis prior to pregnancy if there is less than moderate mitral regurgitation and favorable valve morphology—even in the absence of symptoms [15]. In those individuals that acquire symptoms with pregnancy, percutaneous balloon commissurotomy can also be used to increase mitral valve area and ameliorate retractable symptoms or heart failure. The risk/benefit of radiation exposure to the gravid uterus should be discussed in a multimodality fashion with cardiology, maternal-fetal medicine, and interventional cardiology prior to the procedure. Ideally percutaneous intervention is performed in the second trimester as organogenesis is complete and the cardiac positioning has not been affected by the gravid uterus. Surgical intervention after caesarian section has been reported in the setting of refractory symptoms to medical management, and valvular morphology is not favorable for percutaneous intervention [16].

Mitral regurgitation

As in patients with aortic regurgitation, asymptomatic patients with severe mitral regurgitation and normal left ventricular function are usually able to tolerate pregnancy without any major cardiovascular events. The left atrial and left ventricular dilatation that occurs due to increased preload with pregnancy may decrease the amount of mitral valve prolapse seen during pregnancy [17]. Symptomatic individuals with mitral regurgitation, however, are at increased risk for the development of heart failure with pregnancy and should undergo repair or replacement of the mitral valve before pregnancy.

Prosthetic heart valves

Maternal mortality in women with prosthetic heart valves is increased 12-fold compared to controls [18]. Discussion of valvular replacement options (mechanical or bioprosthethic) should be performed before pregnancy and should include anticoagulation risk for both the fetus and mother. Patients who elect for mechanical replacements should have frequent monitoring of their anticoagulation with an experienced cardiologist. Emergency valve surgery during pregnancy carries increased risk for both the fetus and mother and should be reserved only for those with intractable heart failure symptoms.

Each valvular replacement or repair option has advantages and disadvantages during pregnancy including: risk of anticoagulation to mother and fetus, thromboembolic risk, and bioprosthethic valve degeneration. It is not clear whether pregnancy itself leads to acceleration of prosthetic valve degeneration or whether the young age of these patients is the primary driver. Approximately one third of patients with a bioprosthetic valve who undergo pregnancy will require re-replacement in 10 years [19]. For those individuals with prosthetic valves, a pre-pregnancy plan is recommended if possible. An echocardiogram should be ordered to evaluate baseline prosthetic function and again during pregnancy if symptoms develop.

Warfarin is teratogenic, especially in the first trimester. However, a total daily dose of less than 5 mg was showed to have a lower risk of fetal complications in some studies [20–22]. In the first trimester of pregnancy, the ACC/AHA guidelines recommend continuation of warfarin (if the dose is <5 mg/day) or use of heparin products such as low molecular weight heparin (LMWH) or unfractionated heparin (UFH). If the baseline warfarin dose is greater than 5 mg/day, the ACC/AHA guidelines recommend the use of LMWH or UFH. In the second and third trimesters of pregnancy, warfarin is recommended with titration to therapeutic INR in addition to aspirin [7••]. Warfarin should be switched to UFH around planned vaginal delivery. All heparin products should be temporarily held before planned delivery and restarted after delivery when the patient is deemed safe from bleeding complications.

Anticoagulation management for mechanical heart valves varies with institution, and we avoid warfarin altogether during pregnancy. LMWH does not cross the placenta and can be used with close monitoring of weekly peak and trough anti-Xa levels. We target anti-Xa levels of 0.8 to 1.2 U/mL checked before dose administration and again 4 to 6 h after dose administration [7••]. Monitoring using only anti-Xa plasma peak levels can lead to inappropriate overdosing or underdosing of anticoagulation [23, 24]. Higher than predicted weight-based dosing of LMWH is often needed as the volume of distribution changes in pregnancy. In a recent meta-analysis, thromboembolic complications in those who received prophylaxis with vitamin K antagonists (VKA) and LMWH were 2.7 and 8.7%, respectively [25].

Aspirin is recommended in the ACC/AHA valve guidelines in addition to oral anticoagulation in the second and third trimesters for patients with bioprosthethic or mechanical valves [7••]. Although the data for aspirin plus warfarin in the pregnant population is limited [26], the rate of valve thrombosis in pregnancy increases tenfold over that in the general population. There is evidence that thrombolytic therapy can be used in pregnancy with a high risk of neonatal mortality of 20% [27]. If a women presents in labor fully anticoagulated, this is a situation when caesarian section is indicated to reduce the risk of fetal intracranial hemorrhage.

Summary

Individuals with valvular heart disease should ideally have preconception counseling by a multidisciplinary team consisting of a cardiologist with expertise in pregnancy as well as a maternal-fetal medicine specialist. In situations where valvular disease is discovered during pregnancy, medical management

with close follow-up is recommended for signs and symptoms of heart failure or arrhythmia. Invasive procedures (percutaneous or surgical) are avoided in pregnancy unless absolutely necessary. Multidisciplinary management and communication between cardiology, maternal-fetal medicine, and anesthesiology is recommended to best manage these patients throughout pregnancy.

Compliance with Ethical Standards

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

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

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