CLINICAL PRACTICE

Valvular Heart Disease in Pregnancy

Sharon C. Reimold, M.D., and John D. Rutherford, M.B., Ch.B.

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

A 29-year-old woman with a history of mitral stenosis who has a St. Jude Medical mitral-valve prosthesis presents for evaluation before attempting to conceive. She is concerned about the risks that pregnancy will confer on her and her child. How should she be evaluated and followed?

THE CLINICAL PROBLEM

From the University of Texas Southwestern Medical Center, Dallas.

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Valvular heart disease in young women is most commonly due to rheumatic heart disease, congenital abnormalities, or previous endocarditis and may increase the maternal and fetal risks associated with pregnancy. The likelihood of an adverse outcome is related to the type and severity of maternal valvular disease and the resulting abnormalities of functional capacity, left ventricular function, and pulmonary pressure. Clinical recommendations concerning valvular heart disease and pregnancy are based on limited data from case reports and observational studies or on inferences from data for other groups of patients.

CARDIOVASCULAR PHYSIOLOGY OF PREGNANCY

Normal pregnancy is associated with an increase of 30 to 50 percent in blood volume and a corresponding increase in cardiac output. These increases begin during the first trimester; the levels peak by 20 to 24 weeks of pregnancy and then are either sustained until term or decrease.[1] Concurrently, the heart rate increases by 10 to 20 beats per minute, the stroke volume increases, and there is a substantial reduction in systemic vascular resistance, with decreases in blood pressure. During labor, cardiac output increases; the blood pressure increases with uterine contractions. Immediately after delivery, the cardiac filling pressure may increase dramatically due to the decompression of the vena cava and the return of uterine blood into the systemic circulation. The cardiovascular adaptations associated with pregnancy regress by approximately six weeks after delivery.

Murmurs develop in nearly all women during pregnancy. These murmurs are usually soft, midsystolic, and heard along the left sternal border. Their intensity may increase during pregnancy as cardiac output increases. Cervical venous hums and a continuous murmur due to increased mammary blood flow may also be heard. Echocardiography is warranted when diastolic murmurs, continuous murmurs, or loud systolic murmurs (louder than grade 2 on the 6-point scale) are detected or when murmurs are associated with symptoms or an abnormal electrocardiogram.[2] In normal pregnant women, serial echocardiography usually demonstrates minor increases in the left and right ventricular diastolic dimensions, which remain within the normal range, with a slight decrease in the left ventricular end-systolic dimension and a minimal increase in the size of the left atrium. The state of increased volume also results in increased transvalvular flow velocities. Minor degrees of atrioventricular valve regurgitation are normal.[3]

CONSEQUENCES OF VALVULAR HEART DISEASE DURING PREGNANCY

Although the prevalence of clinically significant maternal heart disease during pregnancy is low (probably less than 1 percent[4]), its presence increases the risk of adverse maternal, fetal, and neonatal outcomes.[5] The American Heart Association and the American College of Cardiology have classified maternal and fetal risk during pregnancy on the basis of the type of valvular abnormality and the New York Heart Association (NYHA) functional class (Table 1).[6] The absolute risk conferred on a given woman by pregnancy also depends on additional clinical factors.

Recent analyses of the outcomes of pregnancy in Canada[4] identified predictors of adverse maternal and fetal outcomes in a heterogeneous group of women with congenital or acquired heart disease (546 women and 599 pregnancies). Approximately 40 percent of the women had a primary valve disorder. Adverse maternal cardiac events (pulmonary edema, sustained bradyarrhythmias or tachyarrhythmias requiring therapy, stroke, cardiac arrest, or death) occurred in 13 percent of completed pregnancies and were significantly more likely among women with reduced left ventricular systolic function (an ejection fraction below 40 percent), left heart obstruction (aortic stenosis with a valve area of less than 1.5 cm^2 or mitral stenosis with a valve area of less than 2.0 cm^2), previous cardiovascular events (heart failure, transient ischemic attack, or stroke), or disease of NYHA class II or higher.[4] These outcomes occurred in 4 percent of the women with none of these risk factors, 27 percent of those with one risk factor, and 62 percent of those with two or more risk factors. The three women who died all had two or more risk factors.

Abnormal functional capacity (NYHA class II or higher) and left heart obstruction were also predictors of neonatal complications, including premature birth, intrauterine growth retardation, respiratory distress syndrome, intraventricular hemorrhage, and death. Other predictors of adverse fetal outcomes included the use of anticoagulant drugs throughout pregnancy, smoking during pregnancy, and multiple gestation. Fetal mortality was 4 percent among pregnancies in women with one or more of these risk factors, as compared with 2 percent among those with none of these risk factors. The risks of adverse fetal outcomes were also sub-

Table 1. Classification of Valvular Heart Lesions According to Maternal, Fetal, and Neonatal Risk.*

Low Maternal and Fetal Risk	High Maternal and Fetal Risk	High Maternal Risk	High Neonatal Risk
Asymptomatic aortic stenosis with a low mean outflow gradient (<50 mm Hg) in the presence of normal left ventricular systolic function	Severe aortic stenosis with or without symptoms	Reduced left ventricular systolic function (left ventricular ejection fraction <40%)	Maternal age <20 yr or >35 yr
Aortic regurgitation of NYHA class I or II with normal left ventricular systolic function	Aortic regurgitation with NYHA class III or IV symptoms	Previous heart failure	Use of anticoagulant therapy throughout pregnancy
Mitral regurgitation of NYHA class I or II with normal left ventricular systolic function	Mitral stenosis with NYHA class II, III, or IV symptoms	Previous stroke or transient ischemic attack	Smoking during pregnancy
Mitral-valve prolapse with no mitral regurgitation or with mild-to-moderate mitral regurgitation and with normal left ventricular systolic function	Mitral regurgitation with NYHA class III or IV symptoms		Multiple gestations
Mild-to-moderate mitral stenosis (mitral-valve area >1.5 cm^2, gradient <5 mm Hg) without severe pulmonary hypertension	Aortic-valve disease, mitral-valve disease, or both, resulting in severe pulmonary hypertension (pulmonary pressure >75% of systemic pressures)		
Mild-to-moderate pulmonary-valve stenosis	Aortic-valve disease, mitral-valve disease, or both, with left ventricular systolic dysfunction (ejection fraction <0.40)		
	Maternal cyanosis		
	Reduced functional status (NYHA class III or IV)		

* Derived from ACC/AHA Guidelines[6] and Siu et al.[4,5] NYHA denotes New York Heart Association.

stantially greater among women older than 35 years of age or younger than 20 years of age than among women between these ages with similar risk factors. Indexes of risk derived from and validated in this population may be used in the counseling of women before conception.

In another cohort including 64 women with valvular heart disease,[7] most adverse maternal outcomes, including heart failure and arrhythmias, occurred in patients with clinically significant mitral or aortic stenosis (valve area, <1.5 cm^2). Premature birth, intrauterine growth retardation, and low birth weight were also more common among the offspring of the women in this subgroup. The fetus is at increased risk for congenital heart disease if the underlying maternal valvular disease is congenital.[8]

Although these studies included few patients with pulmonary hypertension, primary pulmonary hypertension is associated with high maternal mortality (33 to 40 percent), as well as with an increased rate of adverse neonatal events.[9] Secondary pulmonary hypertension due to valvular disease is associated with an increased rate of adverse maternal events, but the absolute risk of such events is unclear. A systolic pulmonary-artery pressure that is more than 75 percent as high as the systemic pressure places the woman at high risk.

STRATEGIES AND EVIDENCE

EVALUATION

The assessment of a woman with clinically significant valvular heart disease should ideally occur before conception and should entail a full cardiac assessment, including echocardiography. The history should focus on the patient's exercise capacity, current or past evidence of heart failure, and associated arrhythmias. Cardiac hemodynamics, including pulmonary pressures and the severity of valve dysfunction, should be assessed by echocardiography. Exercise testing may be useful if the history is inadequate to allow an assessment of functional capacity. During pregnancy, women with valvular heart disease should be evaluated once each trimester and whenever there is a change in symptoms, in order to evaluate any deterioration in maternal cardiac status.[8]

PHARMACOLOGIC TREATMENT

Medical therapy for valvular heart disease in the nonpregnant patient may include the use of vasodilators, diuretics, anticoagulants, and antiarrhythmic agents. During pregnancy, many of these therapies are associated with an increased risk to the fetus, but if the benefits to the mother are thought to outweigh the risks, then they are used (Table 2).[10]

Bacteremia after uncomplicated vaginal delivery occurs in approximately 2 percent of patients.[11] Antibiotic prophylaxis at the time of delivery is not recommended in women with valvular heart disease unless clinically overt infection is present.[12] Patients at high risk for endocarditis may receive antibiotics at the discretion of the physician (Table 2).[12]

SPECIFIC VALVULAR LESIONS

Mitral Stenosis

Rheumatic mitral stenosis is the most common clinically significant valvular abnormality in pregnant women and may be associated with pulmonary congestion, edema, and atrial arrhythmias during pregnancy or soon after delivery. The increased volume load and increased cardiac output associated with pregnancy lead to an increase in left atrial volume and pressure, elevated pulmonary venous filling pressures, dyspnea, and decreased exercise tolerance. Increases in the maternal heart rate decrease the diastolic filling period, further increasing left atrial pressure. Mortality among pregnant women with minimal symptoms is less than 1 percent.[13] In a study of women with mitral stenosis, predictors of adverse maternal outcomes included a reduced mitral-valve area (less than 1.5 cm^2) and an abnormal functional class before pregnancy.[14] Fetal mortality increases with deteriorating maternal functional capacity; fetal mortality is 30 percent when there is NYHA class IV disease in the mother.[15]

For women with mild or moderate symptoms during pregnancy, medical therapy is directed at the treatment of volume overload and includes diuretic therapy, the avoidance of excessive salt, and the reduction of physical activity. Beta-blockers attenuate the increases in heart rate and prolong the diastolic filling period,[16,17] which provides symptomatic benefit.[18] Development of atrial fibrillation requires prompt treatment, including cardioversion. Beta-blockers and digoxin are used for rate control. If suppressive antiarrhythmic therapy is needed, procainamide[19] and quinidine[20,21] are the drugs with which we have the most extensive experience. Because of the increased risk of systemic embolism in patients with mitral stenosis and atrial fibrillation, anticoagulant therapy is indicated.[22,23]

Patients with severe symptoms (NYHA class III or IV) or tight mitral stenosis (a valve area of less

than 1.0 cm²) who undergo balloon mitral valvuloplasty or valve surgery[24] before conceiving appear to tolerate pregnancy with fewer complications than similar women who are treated medically. In patients who present with severe symptoms during pregnancy, successful percutaneous balloon mitral valvuloplasty, performed during the second trimester, has been associated with normal subsequent deliveries and excellent fetal outcomes.[25] Risks to the fetus associated with exposure to radiation may be reduced by avoiding exposure to radiation during the first half of pregnancy.[26] Pregnant women who are to be exposed to radiation should have the uterus shielded and should be informed about the possible risks. Mitral valvuloplasty has also been performed under transesophageal echocardiographic guidance, eliminating these risks. Open cardiac surgery has been performed during pregnancy for severe mitral stenosis. Maternal outcomes are approximately the same as those among nonpregnant patients, but there is fetal loss in 10 to 30 percent of cases.[27]

Vaginal delivery is the usual approach, with the use of epidural anesthesia to achieve effective pain control and with the use of assisted-delivery devices during the second stage of delivery (eliminating the need for pushing). Cesarean section should be performed when there are obstetrical indications for it. Labor is associated with an increase of 8 to 10 mm Hg in the left atrial and pulmonary wedge pressures. Pulmonary arterial catheters have been used successfully before and during delivery to facilitate the management of hemodynamics in women with advanced disease.[28]

Mitral Regurgitation

Mitral regurgitation[29] in young women is most commonly due to mitral-valve prolapse and is usually well tolerated during pregnancy because of the reduction in systemic vascular resistance. Women with symptomatic mitral regurgitation may benefit from mitral-valve surgery — preferably repair[30] — before becoming pregnant. However, left ventricular dysfunction associated with mitral regurgitation is unlikely to improve after surgery[31] and will increase maternal risk during pregnancy.[9] Outcome data that would help to guide clinical decision making in this area are lacking.

Aortic Stenosis

Congenital valvular abnormalities are usually the cause of aortic stenosis in young women,[32] and severe stenosis is poorly tolerated during pregnancy. Patients who are symptomatic or who have a peak outflow gradient of more than 50 mm Hg are advised to delay conception until after surgical correction.[6] Termination of pregnancy should be strongly considered if the patient is symptomatic before the end of the first trimester. Aortic-valve replacement and palliative aortic balloon valvuloplasty have been performed during pregnancy with some associated maternal and fetal risk.[27,33,34]

Aortic Regurgitation

Aortic regurgitation in young women may be due to a dilated aortic annulus (as in Marfan's syndrome), a bicuspid aortic valve, or previous endocarditis. The reduced systemic vascular resistance of pregnancy reduces the volume of regurgitant blood. Isolated aortic regurgitation can usually be managed with vasodilators and diuretics.[6] Women with an abnormal functional capacity or left ventricular dysfunction are predicted to have a high risk of abnormal maternal outcomes, but few data concerning this population are available. The use of angiotensin-converting–enzyme inhibitors should be discontinued during pregnancy,[35] and other agents, such as hydralazine or nifedipine, should be substituted. Clinical and echocardiographic assessment should be performed before conception in women with aortic regurgitation due to Marfan's syndrome; even in the absence of overt cardiac abnormalities, this syndrome predisposes women to unpredictable, but increased, risk during pregnancy.[33,36]

Prosthetic Heart Valves

Bioprostheses are not as durable as mechanical prostheses, although they may eliminate the need for anticoagulant therapy associated with mechanical prostheses. In a review of 232 cases involving women with prosthetic heart valves, the women with mechanical valves had a higher rate of thromboembolism and higher 10-year mortality than those with bioprostheses, despite a lower rate of valve loss (including reoperation and valve-related death).[37] Pregnancy did not appear to increase the rate of failure of mechanical prostheses or homografts,[37] and the deterioration of bioprosthetic valves was not accelerated by pregnancy.[37-39] Pregnancy in a woman with a mechanical valve is associated with an estimated maternal mortality of 1 to 4 percent, with death usually resulting from complications of prosthetic-valve thrombosis.

Table 2. Fetal Effects of, Maternal Indications for, and Risks Associated with Drugs Used in the Treatment of Maternal Valvular Heart Disease.*

Drug	Fetal Effects	Indications in Pregnant Patients with Valve Disease	Risk Category
Diuretics			
Furosemide	Increased urinary sodium and potassium levels	To decrease congestion associated with valvular heart disease	C_m
Antihypertensive agents			
Beta-blockers	Possible decreased heart rate, possible lower birth weight	Hypertension, supraventricular arrhythmias, to control heart rate in women with clinically significant mitral stenosis	D_m
Methyldopa	No major adverse effects	Hypertension	C
Vasodilator agents			
Angiotensin-converting–enzyme inhibitors	Urogenital defects, death, intrauterine growth retardation	Not indicated during pregnancy and should be discontinued	D_m
Hydralazine	No major adverse effects	For vasodilation in cases of aortic regurgitation and ventricular dysfunction	C_m
Nitrates	Possible bradycardia	Rarely used to decrease venous congestion	B–C_m
Anticoagulant and antithrombotic agents			
Warfarin	Hemorrhage, developmental abnormalities when used between wk 6 and 12 of gestation	For anticoagulation of mechanical heart valves, valvular heart disease with associated atrial fibrillation during wk 12–36 of pregnancy	D_m
Unfractionated heparin	Hemorrhage, no congenital defects	For anticoagulation of mechanical heart valves, valvular heart disease with associated atrial fibrillation during wk 6–12 and after wk 36 of pregnancy	C_m
Low-molecular-weight heparin	Hemorrhage	Not currently indicated during pregnancy	D_m
Aspirin	Hemorrhage, prolongation of labor, low birth weight (when taken in high doses)	Low-dose aspirin (81 mg/day) occasionally used as an adjunct in patients with previous embolic events or prosthetic-valve thrombosis	C
Antiarrhythmic agents			
Digoxin	No major adverse effects	For suppression of supraventricular arrhythmias	C
Adenosine	No major adverse effects	For immediate conversion of supraventricular arrhythmias	C_m
Quinidine	High doses may be oxytocic	Occasionally used for suppression of atrial or ventricular arrhythmias	C_m
Procainamide	No major adverse effects	Occasionally used for suppression of atrial or ventricular arrhythmias	C_m
Amiodarone	Hypothyroidism, intrauterine growth retardation, premature birth	Rarely used during pregnancy because of side effects; may be used to suppress atrial or ventricular arrhythmias in high-risk patients	C_m

AREAS OF UNCERTAINTY

As with most matters of concern regarding women with valvular disease who are contemplating becoming pregnant, there are no results of clinical trials to guide the choice of anticoagulant therapy during pregnancy.[6,40-43] With both warfarin and unfractionated heparin, monitoring is required in order to assess whether the antithrombotic effect is adequate, and the effective doses of these drugs change during pregnancy because of changes in intravascular volume and body weight. In a review including 976 women with a total of 1234 pregnancies,[44] the use of any anticoagulant therapy resulted in major bleeding in 2.5 percent of the pregnancies, with bleeding usually occurring at the time of delivery.

Table 2. (Continued.)

Drug	Fetal Effects	Indications in Pregnant Patients with Valve Disease	Risk Category
Antibiotics for prophylaxis against endocarditis†			
Ampicillin	No major adverse effects	Given along with gentamicin to high-risk patients to prevent endocarditis	B
Vancomycin	No major adverse effects	Given along with gentamicin to high-risk patients with allergy to penicillin to prevent endocarditis	C_m
Gentamicin	No major adverse effects	Given along with ampicillin or vancomycin to high-risk patients to prevent endocarditis	C

* Adapted from Briggs et al.[10] The risk categories are defined as follows. For drugs in category B, either studies of animal reproduction have not demonstrated a fetal risk but there have been no controlled studies in pregnant women or studies of animal reproduction have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters). For drugs in category C, either studies in animals have revealed adverse effects on the fetus and there have been no controlled studies in pregnant women or no studies in women or animals are available; these drugs should be given only if the potential benefit justifies the potential risk to the fetus. For drugs in category D, there is evidence of risk to the human fetus, but the benefits from use in pregnant women may be acceptable despite the risk. A subscript m indicates that the manufacturer has rated the risk.

† Antibiotic prophylaxis against endocarditis may be used at the discretion of the treating physician at the time of delivery in high-risk patients. High-risk patients include those with prosthetic cardiac valves, previous bacterial endocarditis, surgically constructed systemic pulmonary shunts or conduits, or complex cyanotic congenital heart disease. Ampicillin should be given intramuscularly or intravenously in a dose of 2.0 g within 30 minutes before delivery; 1 g should be given orally, intramuscularly, or intravenously 6 hours later. Vancomycin should be given intravenously in a dose of 1 g over a period of 1 to 2 hours, beginning 30 minutes before delivery. Gentamicin should be given in a dose of 1.5 mg per kilogram of body weight (not to exceed 120 mg) within 30 minutes before delivery.

In women with mechanical valves,[44] the use of warfarin throughout pregnancy was associated with the greatest maternal protection (risk of thromboembolism, 3.9 percent; risk of death, 1.8 percent), but also with a high rate of fetal loss — approximately 30 percent (including spontaneous abortions, stillbirths, and neonatal deaths). Fetopathic effects of warfarin use (nasal hypoplasia and bone stippling) occurred in approximately 6 percent of cases, and exposure to warfarin between 6 and 12 weeks of gestation was associated with a rate of fetal loss that was twice that associated with the use of unfractionated heparin during this period.

When heparin rather than warfarin was used during the first trimester, the risks of maternal thromboembolism and maternal death more than doubled (to 9.2 percent and 4.2 percent, respectively). The use of adjusted-dose heparin (titrated to a therapeutic activated partial-thromboplastin time) throughout pregnancy was associated with the highest risks of maternal thromboembolism and maternal death (25 percent and 7 percent, respectively).[44] A large proportion of the women had ball-and-cage valves or older single-tilting-disk valves — types of prostheses that are known to carry a high risk of thromboembolism. An increased thrombotic risk associated with heparin has also been observed in other studies, but the adequacy of anticoagulation was not reported.[45] Long-term use of heparin is associated with maternal risks of heparin-associated thrombocytopenia and osteopenia.[37,44]

Low-molecular-weight heparins have been used successfully to treat deep venous thrombosis during pregnancy,[43] are associated with lower risks of thrombocytopenia[46] and osteopenia[47] than unfractionated heparin, and are probably safe for the fetus.[48] However, there are insufficient data from studies of women with prosthetic heart valves to support the efficacy of this therapy or the use of any type of heparin throughout pregnancy.[6,41] Nor has the use of low-molecular-weight heparin been studied in women with atrial fibrillation associated with valvular disease during pregnancy.

GUIDELINES

Guidelines from the American Heart Association and the American College of Cardiology emphasize that, except for pregnancy in women with mitral stenosis, data on outcomes are limited.[6] They recommend that pregnancy be avoided or terminated in women with cyanotic congenital heart disease, pulmonary hypertension, and Eisenmenger's syndrome. They also recommend that women with

Table 3. Recommendations for the Evaluation and Care of Women of Childbearing Age with Mechanical Valve Prostheses Who Are Taking Anticoagulants.*

Before Conception
Clinical evaluation of cardiac functional status and previous cardiac events
Echocardiographic assessment of ventricular and valvular function and pulmonary pressure
Discussion of risks associated with pregnancy
Discussion of risks and benefits associated with anticoagulant therapy
Family or pregnancy planning
Conception
Change to therapeutic, adjusted-dose unfractionated heparin (titrated to a mid-interval therapeutic activated partial-thromboplastin time or anti–factor Xa level) from time of confirmed pregnancy through wk 12
Completion of first trimester
Warfarin therapy, wk 12–36
Week 36†
Discontinue warfarin
Change to unfractionated heparin titrated to a therapeutic activated partial-thromboplastin time or anti–factor Xa level
Delivery
Restart heparin therapy 4 to 6 hr after delivery if no contraindications
Resume warfarin therapy the night after delivery if no bleeding complications

* Information is from ACC/AHA Guidelines,[6] Gohlke-Barwolf et al.,[41] and Ginsberg et al.[42]

† If labor begins while the woman is receiving warfarin, anticoagulation should be reversed and cesarean delivery should be performed.

high-risk lesions undergo full evaluation and care by specialists in this area.

Both European[41] and North American[6] guidelines emphasize that the use of oral anticoagulants throughout pregnancy, targeted to an international normalized ratio (INR) of 2.0 to 3.0, confers the greatest maternal protection[6,41,42] and that heparin used during the first trimester confers a lesser degree of protection. A recent consensus conference[42] recommended that unfractionated or low-molecular-weight heparin could be used until the 13th week of pregnancy, with monitoring of levels of antibody to activated factor X to achieve therapeutic levels. This option was suggested because of medicolegal concern relating to the "off-label" use of warfarin and the risk of embryopathy. The guidelines encourage education of the prospective parents and their involvement in the decision-making process.[6,42]

SUMMARY AND RECOMMENDATIONS

For patients with valvular disease such as the woman described in the vignette, careful clinical assessment and echocardiography are warranted before conception, in order to assess functional capacity and to detect any left ventricular dysfunction or valvular dysfunction. If the patient has abnormal functional capacity, left ventricular dysfunction, valve obstruction, or a history of heart failure or embolic events, she should be counseled regarding the risk of adverse cardiac outcomes. In patients with more than one such risk factor, pregnancy may not be advisable. A patient who becomes pregnant should be seen by a cardiologist once each trimester and more often if complications ensue. Serial echocardiography during pregnancy generally is not warranted.

Patients with prosthetic valves must be counseled regarding the risks and benefits associated with anticoagulant therapy. Although definitive data are lacking,[42] we would recommend the use of warfarin to achieve a target INR of 2.0 to 3.0 throughout most of the pregnancy. The only exceptions are the periods between 6 and 12 weeks of pregnancy and after 36 weeks of pregnancy,[22] when we would opt for the closely monitored use of unfractionated heparin (Table 3).

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