The management of valvular heart disease due to congenital or acquired etiologies in pregnant patients can be challenging. There is an elevated incidence of adverse maternal and fetal outcomes in this patient population. The keys to optimizing pregnancy outcomes are accurate diagnosis of the etiology and severity of valve disease, pre-conception evaluation and counseling, and referral of the highest risk women to centers with expertise in the management of these patients. A multidisciplinary team approach may be warranted, with a cardiologist, obstetrician, and obstetric anesthesiologist. The aim of this paper is to provide a comprehensive review of the management of specific valvular lesions in pregnancy and the role of anticoagulation in pregnancy. An understanding of the normal hemodynamic changes and adaptation of pregnancy is required in order to appreciate the effect of valvular lesions.

**General considerations**

**Hemodynamic changes during pregnancy**

Dramatic changes occur in the cardiovascular system during pregnancy. There is a 30-50% increase in cardiac output by the end of the first trimester, which peaks between the second and third trimesters.\(^1,2\) This increase is primarily due to an increase in stroke volume and in circulating blood volume. During the third trimester, preload reduction may occur due to compression of the inferior vena cava by the gravid uterus. In addition, there is a 15-20% increase in heart rate, which contributes to an increase in cardiac output. However, the placental circulation offers a decrease in systemic vascular resistance, which can be favorable for certain cardiac lesions.\(^1,2\)

**Hemodynamic changes during labor and delivery**

At the time of labor and delivery, there are several changes in the circulatory system that could result in hemodynamic decompensation.\(^1,2\) There is a further increase in heart rate and blood pressure due to pain and anxiety. Changes in fluid balance resulting from an increase in blood volume during each contraction during labor, as well as a lack of inferior vena cava compression contributing to increased preload, both result in a further increase in blood volume, which can result in pulmonary congestion and heart failure.\(^3\) The delivery will involve blood loss. Alterations in the hemodynamic status occur most abruptly within the first 12-24 hours after delivery. Thus, it is essential that patients be monitored during this time in the appropriate setting.

**Symptoms and signs: normal physical exam in the pregnant patient**

The normal physical exam in pregnancy can often mimic disease (Table 1).\(^2,4\) In-
creased plasma volume may result in a systolic flow murmur, which can be heard in most normal pregnant patients. This murmur is usually systolic and soft (usually ≤ grade II/VI). A venous hum can also be heard, which is usually related to increased mammary blood flow. In normal pregnant patients, echocardiographic changes in the form of mild dilation of the left ventricle and left atrium are commonly seen. Trivial valvular regurgitation is commonly seen in the mitral, tricuspid and pulmonic valves. This may be related to the physiologic hemodynamic changes of pregnancy. In addition, mild tricuspid and mitral annular dilatation may be present, which can contribute to mild valvular regurgitation.2

Table 1. Cardiovascular findings in a normal pregnancy.

<table>
<thead>
<tr>
<th>Normal history:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpitations</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Decreased exercise tolerance</td>
</tr>
<tr>
<td>Lower extremity edema</td>
</tr>
<tr>
<td>Orthopnea</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Normal physical exam:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midsystolic murmur at the left base (flow murmur)</td>
</tr>
<tr>
<td>Continuous murmur (mammary souffle)</td>
</tr>
<tr>
<td>Split S1</td>
</tr>
<tr>
<td>Distended or mildly increased neck veins</td>
</tr>
<tr>
<td>Lower extremity edema</td>
</tr>
</tbody>
</table>

Prevalence of valve disease in women of child bearing age

Although cardiac disease complicates less than 1% of pregnancies,5 it can significantly increase the maternal and fetal risk of adverse outcomes.5,6 The development of effective therapy for the treatment of patients during infancy and childhood has resulted in an increased prevalence of adults with congenital heart disease who are of childbearing age (Table 2). Moreover, rheumatic heart disease remains a common disease for patients worldwide, despite an overall decline of the prevalence in Europe and North America.7 Other causes of valve disease in younger women are included in Table 2. Prosthetic valves are increasingly seen in women of childbearing age. Those with mechanical prostheses pose unique challenges due to anticoagulation issues. The options for anticoagulation are suboptimal in pregnant women, as will be discussed later in this review. Concerns over accelerated valvular deterioration have been raised in patients with bioprostheses,8 although not all studies have borne this out.9

Table 2. Valvular lesions in women of child bearing age.

<table>
<thead>
<tr>
<th>Valvular regurgitation:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic regurgitation</td>
</tr>
<tr>
<td>Congenital (i.e. bicuspid aortic valve)</td>
</tr>
<tr>
<td>Rheumatic</td>
</tr>
<tr>
<td>Connective tissue disorder (Marfan syndrome)</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
</tr>
<tr>
<td>Myxomatous</td>
</tr>
<tr>
<td>Congenital</td>
</tr>
<tr>
<td>Rheumatic</td>
</tr>
<tr>
<td>Pulmonic regurgitation</td>
</tr>
<tr>
<td>Residual after pulmonic valve balloon valvotomy</td>
</tr>
<tr>
<td>Residual after congenital surgical correction (i.e. tetralogy of Fallot)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Valvular stenosis:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic stenosis</td>
</tr>
<tr>
<td>Congenital</td>
</tr>
<tr>
<td>Rheumatic</td>
</tr>
<tr>
<td>Subaortic membrane</td>
</tr>
<tr>
<td>Mitral stenosis</td>
</tr>
<tr>
<td>Congenital</td>
</tr>
<tr>
<td>Rheumatic</td>
</tr>
<tr>
<td>Pulmonic stenosis</td>
</tr>
<tr>
<td>Congenital</td>
</tr>
<tr>
<td>Isolated pulmonic valvar stenosis</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prosthetic valves:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioprosthesis</td>
</tr>
<tr>
<td>Mechanical</td>
</tr>
</tbody>
</table>

Diagnostic evaluation

The evaluation of patients with cardiovascular disease should ideally begin prior to conception (Table 3),2,4 so that appropriate evaluations can be made without putting the fetus or mother at risk. A detailed history and physical exam, assessment of functional capacity, and a 12-lead EKG are essential. Echocardiography is indicated in women with a history of valvular or congenital heart disease, significant dyspnea, any signs of heart failure, any systolic murmur > grade 2, or any diastolic murmur. A complete echocardiogram with Doppler is necessary to identify the etiology and degree of valvular regurgitation and/or stenosis, degree of pulmonary hypertension, and, if present, aortic root dilatation. Importantly, the left ventricular systolic function can also be quantified. Patients with prosthetic valves may benefit from a baseline echocardiogram prior to pregnancy, so that changes in the gradients across a prosthesis can be carefully followed. Exercise stress...
testing can be useful in order to quantify a patient’s functional capacity. However, this should ideally be performed prior to pregnancy. Functional capacity is an important predictor of the ability to tolerate a pregnancy, regardless of the underlying lesion. In women with significant valve disease, the normal hemodynamic changes of pregnancy can precipitate cardiac symptoms in previously stable women, or may exacerbate symptoms in those with mild baseline symptoms.

Table 4 presents a potential risk assessment and management approach during pregnancy. Patients often require frequent monitoring, with a careful history and physical examination, especially if new symptoms develop or if a patient is deemed to be at high risk from a cardiac perspective. Serial echocardiography may be helpful when new signs or symptoms develop. During the antepartum period, patients with mild valvular disease need to be seen monthly or every other month until 28-30 weeks, after which they may require monitoring every 2 weeks or even weekly. Patients with moderate to severe valvular disease should be seen every 2 weeks until 28-30 weeks, after which they should be seen weekly. Hemodynamic changes intensify after the 26th-28th week, which is the most critical period along with the delivery.

Predictors of high maternal and fetal morbidity

Several studies have assessed the maternal and fetal outcomes of pregnant patients with congenital or acquired valvular disease and have identified important predictors of adverse outcome. Hameed et al11 studied 46 pregnancies in 44 patients with valvular heart disease and found that these patients had marked clinical deterioration and morbid events in the mother (congestive heart failure, need for hospitalization, initiation or increase in cardiac medications and atrial arrhythmias) as well as the fetus (intrauterine growth retardation, low birth weight and prematurity). A clear relationship was found between the severity of mitral or aortic stenosis and adverse maternal and fetal outcomes. Patients with mild mitral or aortic stenosis had outcomes comparable to normal controls.

Pre-pregnancy New York Heart Association (NYHA) functional class and the severity of mitral stenosis were the two main predictors of adverse maternal and fetal outcomes. Leśniak-Sobelga12 studied 259 pregnancies, all of which had valvular disease (158 with mitral disease, 54 with aortic disease, and 47 with prosthetic heart valves). Mitral stenosis was the most common acquired valve disease. Pregnant patients with critical mitral valve stenosis form a high-risk group who are at significantly increased risk of life-threatening complications. In women with severe aortic stenosis, pregnancy can lead to sudden deterioration. Cardiac complications can be expected in patients with left ventricular enlargement and depressed ventricular systolic function. Factors predicting a successful course of pregnancy and labor in patients with prosthetic valves are adequate left ventricular function, properly functioning valves, and effective anticoagulation.

Siu et al5, 6 studied 562 pregnancies, with valvular heart disease being the primary cardiac disease in 18% of these. Primary cardiac events were defined as any of the following: pulmonary edema (documented on chest radiograph or by crackles heard over more than one third of the posterior lung fields), sustained sympto-
matic tachyarrhythmia or bradyarrhythmia requiring treatment, stroke, cardiac arrest, or cardiac death. Secondary cardiac events were defined as a decline in NYHA class (≥2 classes) compared with baseline, or need for urgent invasive cardiac procedures during pregnancy or within 6 months after delivery. This group identified four predictors of primary cardiac events: prior cardiac event (heart failure, transient ischemic attack, or stroke before pregnancy) or arrhythmia; baseline NYHA class >II or cyanosis; left heart obstruction (mitral valve area <2 cm², aortic valve area <1.5 cm², or peak left ventricular outflow tract gradient >30 mmHg by echocardiography); and reduced systemic ventricular systolic function (ejection fraction <40%). A primary or secondary cardiac event, or both, occurred in 99 pregnancies (17%). The four predictors of primary cardiac events were also predictive of the combined likelihood of either a primary or secondary cardiac event. Five predictors of neonatal events were identified: NYHA class >II or cyanosis during the baseline prenatal visit, maternal left heart obstruction, smoking during pregnancy, multiple gestations, and use of anticoagulants throughout pregnancy.

In a subsequent study of 301 pregnancies, Siu et al demonstrated the interaction between maternal obstetric and cardiac risk factors in predicting neonatal adverse events. Pregnant women with heart disease are at increased risk for both neonatal and cardiovascular complications. The risk for neonatal adverse events in pregnant women with heart disease is highest in those with both obstetric (maternal age >35 or <20 years, smoking, multiple gestation) and cardiac (poor maternal functional class, cyanosis, and left heart obstruction) risk factors for neonatal complications. A summary of these findings can be found in Table 5.

Management considerations

Labor and delivery

Multiple studies have shown that vaginal delivery is safe and well tolerated in most patients with cardiovascular disease and specifically with valvular heart disease. However, the timing and mode of delivery should be decided upon prior to delivery, jointly with a multidisciplinary team of cardiologists, obstetricians, and obstetric anesthesiologists. For most patients with valvular heart disease, adequate anesthesia and a shortened second stage of labor is safe and can be applied in the majority of patients. Cesarean section is potentially associated with a higher rate of complications. It is usually recommended for obstetric indications, and occasionally in a patient with cardiac instability. Hemodynamic monitoring during labor is recommended in symptomatic patients and in patients with moderate or severe valvular stenosis, left ventricular dysfunction, and pulmonary hypertension.

Table 5. Risk stratification for pregnant patients with valvular disease.

<table>
<thead>
<tr>
<th>High risk of adverse maternal and fetal outcomes:</th>
<th>Low risk of adverse maternal and fetal outcomes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any prior cardiac event or arrhythmia</td>
<td>Asymptomatic mild or moderate aortic stenosis (peak gradient &lt;25 mmHg and aortic valve area &gt;1.5 cm²)</td>
</tr>
<tr>
<td>NYHA Class &gt;2 or cyanosis</td>
<td>Asymptomatic mild mitral stenosis (MV area &gt;1.5 cm², mean gradient &lt;5 mmHg)</td>
</tr>
<tr>
<td>Systemic ventricular dysfunction (ejection fraction &lt;40%)</td>
<td>NYHA functional class I or II, mitral regurgitation with normal LV systolic function (EF &gt;50%)</td>
</tr>
<tr>
<td>Pulmonary hypertension (PA systolic pressure &gt;50% systemic pressure), whether isolated or associated with severe valve disease</td>
<td>NYHA functional class I or II aortic regurgitation with normal LV systolic function</td>
</tr>
<tr>
<td>Left heart obstruction</td>
<td>Regurgitation or stenosis of left heart valve without significant pulmonary hypertension</td>
</tr>
<tr>
<td>Severe aortic stenosis (valve area &lt;1 cm², Doppler jet velocity &gt;4 m/s)</td>
<td>Mild or moderate pulmonic stenosis</td>
</tr>
<tr>
<td>Symptomatic or severe mitral stenosis</td>
<td></td>
</tr>
<tr>
<td>Severe aortic or mitral regurgitation with NYHA Class III or IV symptoms</td>
<td></td>
</tr>
<tr>
<td>Mechanical prosthetic valve requiring anticoagulation</td>
<td></td>
</tr>
<tr>
<td>Marfan syndrome with or without aortic and mitral regurgitation</td>
<td></td>
</tr>
</tbody>
</table>

EF – ejection fraction; MV – mitral valve; NYHA – New York Heart Association; PA – pulmonary artery.
Antibiotic prophylaxis has been indicated in patients with valvular disease at the time of delivery because of the high incidence of bacteremia (and the resultant high maternal and fetal mortality) and the potential risk of endocarditis.15,16 However, the most recent American Heart Association/American College of Cardiology practice guidelines for valvular heart disease do not include uncomplicated vaginal or cesarean delivery as an indication for antibiotic prophylaxis.17 Patients who have a history of endocarditis, a prosthetic cardiac valve, or are within six months of a percutaneous device placement would remain candidates for antibiotic prophylaxis under the 2006 guidelines and 2008 focused update.17,18 However, many institutions do not agree with this policy, as the rate of bacteremia may be higher than previously reported.14 The recommended regimens for antibiotic prophylaxis include ampicillin (2.0 g intramuscular [IM] or intravenous [IV]) plus gentamycin (1.5 mg/kg, not to exceed 120 mg) given at initiation of labor or within 30 minutes of a cesarean section, followed by ampicillin (1 g IM or IV) or amoxicillin (1 g orally) six hours later. For patients who are allergic to ampicillin and amoxicillin, vancomycin can be substituted (1 g IV over 1-2 hours).14,17

Postpartum concerns

Table 7 describes some of the concerns for the postpartum cardiac patient. Medical therapy should be optimized, particularly during the initial 24-48 hours postpartum. A discussion of contraception should take place before the patient leaves the hospital.

Table 7. Postpartum concerns.

<table>
<thead>
<tr>
<th>Specific valve lesions (Figure 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mitral stenosis</strong></td>
</tr>
</tbody>
</table>

Mitral stenosis (MS) is the most common acquired valvular lesion encountered in pregnant women and is almost invariably caused by rheumatic heart disease.8,10,14 There is a significant increase in the transmural gradient during pregnancy due to the increase in the heart rate, circulating blood volume and cardiac output. Patients who were asymptomatic prior to pregnancy can experience dyspnea, decreased exercise capacity, orthopnea, paroxysmal nocturnal dyspnea and pulmonary edema during pregnancy. An increase in left atrial and pulmonary pressures contributes to atrial wall stress and the development of atrial arrhythmias. Both maternal5,6,8,19,20 and fetal5,6,19 outcomes are directly related to the severity of MS and the pre-pregnancy NYHA functional class. The fetal morbidity (intrauterine growth retardation, low birth weight, prematurity, fetal/neonatal death) has been estimated at approximately 33% in patients with severe MS compared with 28% in patients with moderate MS and 14% in patients with mild MS.12 Despite the reported morbidity, absolute mortality appears to be low.19,21

Medical therapy

Many patients with moderate or severe mitral stenosis can be managed successfully with medical therapy, which includes strict control of heart rate, volume status and frequent monitoring.13,19 The two goals of medical therapy are to reduce the heart rate and reduce the left atrial pressure. Restriction of physical activity effectively reduces the heart rate. Heart rate reduction can be achieved with beta blockers or calcium channel blockers. Metoprolol is the preferred beta blocker, since fetal intrauterine growth retardation, bradycardia and death have been reported with atenolol use.22 Verapamil is preferred over diltiazem, which has been associated with adverse fetal effects. Digoxin can be used in patients with atrial fibrillation for control of ventricular rate and is generally considered safe, well tolerated and has few adverse fetal effects. Reduction of left atrial pressure is achieved by the use of diuretics. However, caution must be exercised to avoid uteroplacental hypoperfusion associated with the use of diuretics, since this is directly related to adverse fetal outcomes. Amiodarone is contraindicated during pregnancy and should not be used for control of ventricular rate.17 Prophylactic anticoagulation with warfarin or lovenox can be considered for patients with severe left atrial dilation and...
Figure 1. A 34-year-old woman, gravida one para zero (G1P0), who presented at 25 weeks pregnant with a murmur. A: Rheumatic mitral stenosis is present. B: Mean forward flow gradient across the mitral valve. C: Moderate aortic regurgitation (rheumatic etiology). D: Mild aortic stenosis is present. E: Moderate tricuspid regurgitation, with top normal pulmonary artery systolic pressure.

severe mitral stenosis despite the presence of sinus rhythm, because of the hypercoagulable state of pregnancy.17

Hemodynamic monitoring is indicated during labor and delivery in patients with moderate to severe mitral stenosis in order to optimize left atrial pressure and avoid the development of pulmonary edema. Epidural anesthesia is recommended to reduce fluctuations in heart rate and cardiac output. Shortening of the second stage of labor and assisted delivery is strongly recommended. Most of the studies described above have performed cesarean sections for obstetric indications.

Role of percutaneous balloon mitral valvuloplasty

For patients who are refractory to medical therapy, and remain in NYHA Class III/IV, percutaneous bal-

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loon mitral valvuloplasty (PBMV) can be performed during pregnancy. It most commonly necessary after the 28th week of pregnancy. Several studies have demonstrated the efficacy of this procedure in experienced centers. Most patients return to NYHA I/II and remain in that class until the end of pregnancy. Consequently, there is a significant reduction of maternal morbidity. Complications such as thromboemboli, stroke, pericardial effusion, atrial arrhythmias and new onset mitral regurgitation have been reported. Severe mitral regurgitation requiring mitral valve repair or replacement is rare. Other complications include excessive blood loss, uterine contractions and precipitous labor. In addition, PBMV is associated with some unavoidable exposure to ionizing radiation. Adequate pelvic and abdominal shielding of radiation is necessary. The dose to the fetus is far below the dose at which therapeutic abortion is recommended. The procedure should be avoided in the first trimester and must be performed by experienced operators. Fluoroscopy should be minimized and the procedure should be assisted by echocardiography and Doppler instead. The use of the Inoue balloon catheter (Toray, Houston, Texas) seems to be preferred, in view of its shorter procedure times and hence less radiation exposure for the fetus.

Should PBMV be performed prophylactically to improve fetal outcomes?

Patients who have severe mitral stenosis or those who are symptomatic with moderate to severe mitral stenosis should have either PBMV or mitral valve replacement before conception. These patients do very well, having favorable maternal and fetal outcomes with reduced clinical deterioration and reduced need for initiation of pharmacologic therapy. Several studies have documented excellent fetal outcomes with normal growth and development at long-term follow up after PBMV. However, other studies have shown no difference in fetal outcomes, despite improvement of maternal functional class and hemodynamics. Although prematurity has been linked to the onset of hypertension, diabetes and neurocognitive delays, percutaneous balloon mitral valvuloplasty is not recommended to improve fetal outcomes in patients with moderate to severe mitral stenosis. There is still a potential risk to the fetus from unavoidable ionizing radiation, and therefore PBMV is not recommended for prophylactic use during pregnancy. This procedure is currently reserved only for medically refractory patients with moderate to severe mitral stenosis.

Mitral valve surgery

Studies have compared the efficacy of PBMV and open mitral commissurotomy, as well as the associated maternal and fetal outcomes. Although both strategies appear to be efficacious, the fetal mortality is up to 35% with open mitral commissurotomy. Specific predictors of adverse fetal outcomes have not been identified. Given the high maternal morbidity and fetal mortality of surgery, PBMV is recommended as the procedure of choice in patients with favorable valve anatomy. In a review of the outcome of cardiovascular surgery in pregnant women from 1984-1996, a 9% maternal mortality and 29% fetal or neonatal mortality was reported. The duration of pregnancy at the time of surgery, length of cardiopulmonary bypass, and temperature apparently did not influence fetal or neonatal outcome.

Mitral regurgitation

The most common etiologies of mitral regurgitation in the pregnant woman are mitral valve prolapse and rheumatic heart disease. Mitral regurgitation without left ventricular dysfunction is well tolerated during pregnancy because of the fall in the systemic vascular resistance with the addition of the placental circulation. The mainstay of management in patients who are symptomatic due to mitral regurgitation and left ventricular dysfunction is afterload reduction and diuretics. Afterload reduction is not indicated in patients with normal or low blood pressure. Hydralazine and nitrates are safe and well tolerated. Angiotensin-converting-enzyme inhibitors as well as angiotensin receptor blockers are highly teratogenic and therefore contraindicated during pregnancy.

Aortic stenosis

Congenital aortic stenosis (AS) is the most common cause of aortic stenosis in pregnant patients. Rheumatic aortic valve disease is less common and frequently occurs in combination with mitral valve disease. Cases with subvalvular and supravalvular AS during pregnancy have been reported. Most patients with mild to moderate AS have favorable pregnancy outcomes. In fact, patients with a valve area >1.0 cm² tolerate pregnancy well, provided early diagnosis and close follow up is ensured. However, patients
with moderate and severe aortic stenosis can deterio-
rate rapidly, with the development of congestive heart
failure (44% of patients), arrhythmias (25%), need to
commence or increase cardiac medications (33%), and
hospitalization (33%). Maternal mortality is rare. In
addition, an increased incidence of fetal intrauterine
growth retardation, respiratory distress, prematurity
and low birth weight has been observed in mothers with
moderate or severe AS.

Patients with severe AS, or those who are symp-
tomatic with AS and desire a pregnancy, should un-
dergo balloon valvuloplasty or valve replacement pri-
or to conception. The medical management of severe
AS during pregnancy is suboptimal, and mainly involves
diuretics. In patients with medically refractory severe
symptoms, termination of the pregnancy, if early, or re-
pair of the valve by either percutaneous balloon valvu-
loplasty or valve replacement should be consid-
ered. Due to the high fetal mortality with aortic valve
replacement, balloon aortic valvuloplasty is preferred.

Hemodynamic monitoring is strongly recommend-
ed for labor and delivery in patients with moderate to
severe aortic stenosis. Vaginal delivery is preferred
with an assisted second stage of labor. Silversides et
al reported that 67% of patients were successfully de-
ivered vaginally in a total of 49 pregnancies in women
with aortic stenosis, with cesarean delivery in the re-
mainder. Epidural and spinal anesthesia should be used
with caution, given the risk of lowering the systemic vas-
cular resistance, which is poorly tolerated in patients
with moderate or severe AS. General anesthesia re-
ains the preferred technique for cesarean section in
patients with aortic stenosis.

Aortic regurgitation

Aortic regurgitation may be due to a congenital bicus-
pid valve, previous endocarditis, rheumatic heart dis-
case or aortic annular dilation. As in the case of mi-
tral regurgitation, aortic regurgitation without left ven-
tricular dysfunction is usually well tolerated, since
the placental circulation contributes to a decrease in after-
load. The higher resting heart rate during pregnancy
shortens diastolic time and hence the degree of regurgi-
tation. In symptomatic patients with severe aortic re-
gurgitation and left ventricular dysfunction, manage-
ment includes salt restriction, afterload reduction, di-
uretics and digoxin. Hydralazine and nitrates can be
used for afterload reduction. Asymptomatic patients
with severe aortic regurgitation and normal left ventric-
ular systolic function who desire a pregnancy will do

well and should not be considered for prophylactic
valve surgery prior to pregnancy.

Pulmonic stenosis

The etiology of pulmonic stenosis is mostly congenital
and valvular, although it can be subvalvular, supravalvu-
lar, or the result of homograft deterioration as part of a
Ross procedure. Patients with severe pulmonic stenosis
have maternal and fetal outcomes comparable to nor-
mal controls, according to limited data. Balloon
valvuloplasty is rarely indicated in a pregnant patient
with pulmonic stenosis. Vaginal delivery is usually safe
and well tolerated.

Prosthetic valve considerations

Selection of prosthetic valve in women of childbearing
age

The selection of a prosthetic heart valve in women of
childbearing age remains challenging and needs to be
individualized. The bileaflet mechanical valves offer a
superior record of durability, an excellent hemodynam-
ic profile, and a relatively small risk of bleeding and
thromboembolic complications with careful anticoagu-
ation. Durability is a major factor in young patients.
However, if compliance with anticoagulation is a con-
cern, or for those patients in whom close follow up is
not possible, a tissue prosthesis is an option. Deteriora-
tion of bioprosthetic heart valves during pregnancy has
been reported in several studies, but has not been con-
irmed by others. Although most available data
might suggest accelerated structural valve deterioration
in pregnancy, this may also reflect the well established
deterioration of tissue valves in young individuals.

Anticoagulation in a pregnant patient with prosthetic
heart valve

Anticoagulation is a major difficulty in the manage-
ment of a pregnant patient with a mechanical pros-
thesis. Anticoagulation poses significant risks to the
pregnant woman (uterine hemorrhage) and to the fe-
tus (abortion, fetal loss, intraventricular hemorrhage
and embroyopathy if warfarin is used). However, the
risks of maternal thromboembolism and death are
high with inadequate anticoagulation, especially in
the hypercoagulable setting of pregnancy (Figure 2).
The hypercoagulable state appears to be due to de-
creased activity of proteins C and S. This is of par-
ticular importance in patients with atrial fibrillation and mechanical heart valves. The type and position of the valvular prosthesis are of critical importance in the selection of anticoagulation in the pregnant woman. Any treatment regimen should be undertaken after full discussion of the risks, benefits, and alternatives with the patient and her family. Patients and families need to understand that there is no optimal approach. Heparin use in the first trimester may be less safe, and may result in valvular thrombosis, bleeding, and/or thromboembolic complications. Moreover, risks to the mother also pose a risk to the fetus. It is difficult to make firm recommendations regarding an anticoagulation strategy, since no randomized trials exist on this subject. One approach to anticoagulation that can be used in pregnant patients, endorsed by the American College of Cardiology/American Heart Association (ACC/AHA) Task Force report in 2006, involves dividing patients into higher risk (history of thromboembolism or an older generation mechanical prosthesis in the mitral position) and low risk (no history of thromboembolism, newer generation mechanical prosthesis) categories. The potential options include: 1) low molecular weight heparin (LMWH) or unfractionated heparin (UFH) between 6-12 weeks, warfarin with a target INR of 2-3 between week 12-36, and then switching to LMWH or UFH after week 36; 2) dose-adjusted UFH throughout pregnancy (intravenously continuous or subcutaneously); or 3) dose-adjusted LMWH throughout pregnancy. Addition of low dose-aspirin can be considered. These recommendations say that warfarin should be stopped after week 35. In addition, they consider the risk of warfarin embryopathy unacceptable to most women and have suggested an alternative of UFH or LMWH. The most recent recommendations, published in 2008 as part of the American College of Chest Physicians (ACCP) consensus on antithrombotic therapy in pregnancy, recommend dose-adjusted LMWH twice daily throughout pregnancy, adjusted-dose UFH throughout pregnancy, or one of these two regimens until the thirteenth week, with warfarin substitution until close to delivery prior to restarting UFH or LMWH. The guideline statement recommends that if a patient is deemed to be at very high risk for thromboembolism and there are concerns about the efficacy and safety of LMWH or UFH, warfarin can be continued throughout pregnancy and replaced with LMWH or UFH close to delivery. A thorough discussion of the risks and benefits
should be documented. Elkayam and Bitar\textsuperscript{39} have combined these two approaches, as shown in Table 8.

**Warfarin**

Warfarin affords the greatest protection against maternal thromboembolism and death in patients with prosthetic heart valves. Chan et al\textsuperscript{42} performed a systematic overview of the various anticoagulation regimens in 1234 pregnancies in patients with older and newer generation mechanical prostheses. The incidence of maternal thromboembolism was lowest (3.9\%) in those given warfarin throughout pregnancy, compared with 9.2\% in the regimen receiving heparin in the first trimester followed by anticoagulants and 25\% in the regimen using heparin throughout pregnancy. The incidence of maternal death was lowest (1\%) in those given warfarin throughout pregnancy, compared with 4.2\% in the regimen receiving heparin in the first trimester followed by anticoagulants and 6.7\% in the regimen using heparin throughout pregnancy. Warfarin use has been associated with fetal wastage and congenital anomalies, which include nasal hypoplasia and epiphyseal stippling. Furthermore, the incidence of fetal intraventricular hemorrhage—especially during forceps extraction—was high. The incidence of fetal wastage was high (33.6\%) in those given warfarin throughout pregnancy, compared with 26.5\% in the regimen receiving heparin in the first trimester followed by warfarin and 42.9\% in the regimen using heparin throughout pregnancy.\textsuperscript{42}

The incidence of warfarin embryopathy has been debated, with a wide range of incidences (5-67\%) reported in the literature,\textsuperscript{30,42,44} but a range of 4-10\% appears to be a reasonable estimate based on the most recent information.\textsuperscript{46,47} However, to most women this is still an unacceptable risk. Some investigators have concluded that the risk of warfarin embryopathy is lower when the daily dose is less than 4 mg.\textsuperscript{48} However, others found the risk of warfarin embryopathy to be independent of warfarin dose.\textsuperscript{49} Warfarin is probably safe during the first 6 weeks. Most women will opt to change to another form of anticoagulation from weeks 6-12 to reduce the risk of warfarin embryopathy. Patients are then switched back to warfarin at week 12, until week 36. Warfarin should be switched to heparin no later than 36 weeks because of the high incidence of premature labor in patients with prosthetic heart valves. Warfarin should be switched over to either continuous UFH, dose-adjusted subcutaneous UFH or dose-adjusted LMWH after the 36th week to avoid bleeding complications during labor and delivery.\textsuperscript{17,44}

**Unfractionated heparin**

UFH does not cross the placenta and is not teratogenic. There is a lower incidence of fetal complications at the

<table>
<thead>
<tr>
<th>Table 8. Recommended approach for anticoagulation prophylaxis in women with prosthetic heart valve during pregnancy. Reprinted from reference 53, with permission from Sage Publications.</th>
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<tbody>
<tr>
<td><strong>Higher Risk</strong></td>
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<tr>
<td>First generation PHV (e.g. Starr-Edwards, Bjork Shiley) in the mitral position, atrial fibrillation, history of TE on anticoagulation</td>
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<tr>
<td>Warfarin (INR 2.5–3.5) for 35 weeks, followed by UFH (mid-interval aPTT &gt; 2.5) or LMWH (pre-dose anti-Xa ~ 0.7) + ASA 80–100 mg q.d.</td>
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<tr>
<td>OR</td>
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<tr>
<td>UFH (aPTT 2.5–3.5) or LMWH (pre-dose anti-Xa ~ 0.7) for 12 weeks, followed by warfarin (INR 2.5–3.5) to 35th week, then UFH (aPTT &gt; 2.5) or LMWH (pre-dose anti-Xa ~ 0.7) + ASA 80–100 mg q.d.</td>
</tr>
</tbody>
</table>

aPTT – activated partial thromboplastin time; ASA – acetylsalicylic acid; INR – international normalized ratio; LMWH – low molecular weight heparin; PHV – prosthetic heart valve; SC – subcutaneous; TE – thromboembolism; UFH – unfractionated heparin.
expense of an increase in maternal thromboembolism and death. A high incidence of maternal thromboembolism and death has been reported both by Sadler and Salazar. These adverse outcomes may be attributed partly to inadequate anticoagulation and lack of monitoring of activated partial thromboplastin time (aPTT). Continuous IV heparin offers more consistent anticoagulation and is recommended in high-risk patients by the ACC/AHA guidelines, but it increases the risk of infection, endocarditis, and osteoporosis. Aggressive dose-adjusted subcutaneous heparin can also be used. The aPTT response to heparin is diminished during pregnancy due to increased levels of factor VIII and fibrinogen. Heparin is given every 12 hours subcutaneously with a mid-interval (6 hours after dosing) aPTT ≥2 × control levels. Strict and frequent monitoring is essential.

Low molecular weight heparin

LMWH has been offered as an alternative to heparin. As with UFH, it does not cross the placenta. It offers potential advantages, such as a lower incidence of bleeding complications, less osteoporosis, predictable dose response, superior bioavailability, a longer half-life, and a lower rate of spontaneous abortion when compared to UFH. A higher incidence of maternal thromboembolism and death has been noted. However, detailed review revealed that these adverse outcomes were related to inadequate dose, lack of monitoring or subtherapeutic anti-Xa levels. The prior warning by the manufacturers regarding the use of LMWH in patients with prosthetic heart valves has been rephrased to state that “use of Lovenox for thromboprophylaxis in pregnant women with mechanical heart valves has not been adequately studied.”

The dose requirement for LMWH changes during pregnancy as a result of changes in weight and volume of distribution. As per the ACCP recommendations, the target anti-Xa level 4 hours after dosing is around 1.0 U/ml. Barbour demonstrated the importance of measuring trough levels, which were subtherapeutic with peak levels of around 1.0 U/ml. Furthermore, pre-dose subtherapeutic anti-Xa levels have been associated with maternal thromboembolism. Therefore, routine measurement and maintenance of trough levels within a range of 0.6 to 0.7 U/ml in patients with prosthetic heart valves is recommended. Elkayam et al also recommend measuring peak levels of anti-Xa (<1.5 U/ml) to avoid excessive anticoagulation. LMWH should be withdrawn 18-24 hours prior to elective delivery to reduce the chance of spinal hematoma during epidural catheter insertion.

In summary, the decision regarding the choice of anticoagulation needs to be made after full discussion with patient and family regarding the risks, benefits and alternatives of each regimen.

References