CME

Clinical Expert Series

Maternal Cardiac Disease

Update for the Clinician

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Heart disease complicates more than 1% of pregnancies and is now the leading cause of indirect maternal deaths. The spectrum and severity of heart disease observed in reproductive-aged women is changing. Today, congenital heart disease accounts for more than half of cardiac disease in pregnancy, and ischemic heart disease is on the rise as a result of obesity, hypertension, diabetes, and delayed childbearing. Pregnancy is still contraindicated in women with pulmonary hypertension, severe systemic ventricular dysfunction, dilated aortopathy, and severe left-sided obstructive lesions, but advances in medical and surgical management have resulted in an increasing number of patients with congenital heart defects reaching childbearing age who are interested in pregnancy. A multidisciplinary approach can best determine whether acceptable outcomes can be expected and what management strategies may improve the prognosis for pregnant women with heart disease.

(Obstet Gynecol 2012;119:345–59)
DOI: 10.1097/AOG.0b013e318242e260

The spectrum of cardiac disease in reproductive-aged women is changing. Although rheumatic heart disease remains a health issue among recent immigrants, congenital heart disease now comprises more than 50% of cardiac lesions observed during pregnancy in developed countries.[1] Hospitalizations for congenital heart disease, arrhythmias, cardiomyopathy, and congestive heart failure in pregnancy have steadily increased in the United States.[2] Postpartum hospitalizations for heart disease tripled from 1995–1997 to 2004–2006, with the bulk of admissions related to life-threatening events such as acute myocardial infarction and cardiac arrest.[2] Heart disease now complicates more than 1% of pregnancies and accounts for 20% of nonobstetric maternal deaths.[2,3]

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Continuing medical education for this article is available at http://links.lww.com/AOG/A278.

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Financial Disclosure
The author did not report any potential conflicts of interest.

ISSN: 0029-7844/12

Potential explanations for the increase in cardiac disease in pregnancy include the rise in obesity, hypertension, and diabetes in young adults and delayed childbearing as well as survival of women with congenital heart disease into adulthood. With advances in surgical and medical treatment of various cardiac conditions, more women with congenital and acquired heart disease are choosing to become pregnant. Older women pursuing pregnancy may have unrecognized cardiovascular conditions such as valvular, myocardial, and coronary artery disease. Although maternal mortality from hemorrhage and hypertensive disorders has steadily decreased in developed countries, the proportion of pregnancy-related deaths attributed to cardiovascular disease has increased.[4] Cardiomyopathies, pulmonary hypertension, aortic dissection, and myocardial infarction are now leading cardiac causes of maternal mortality.[5] In addition to maternal risks, heart disease can have adverse effects on fetal development, growth, and survival.[6] The changing complexity of heart disease in pregnancy poses a significant challenge to the busy health care practitioner.

General Considerations

Preconception Counseling

There is often scant evidence to support recommendations regarding childbearing given to women with cardiac disease. However, preconception counseling pro-

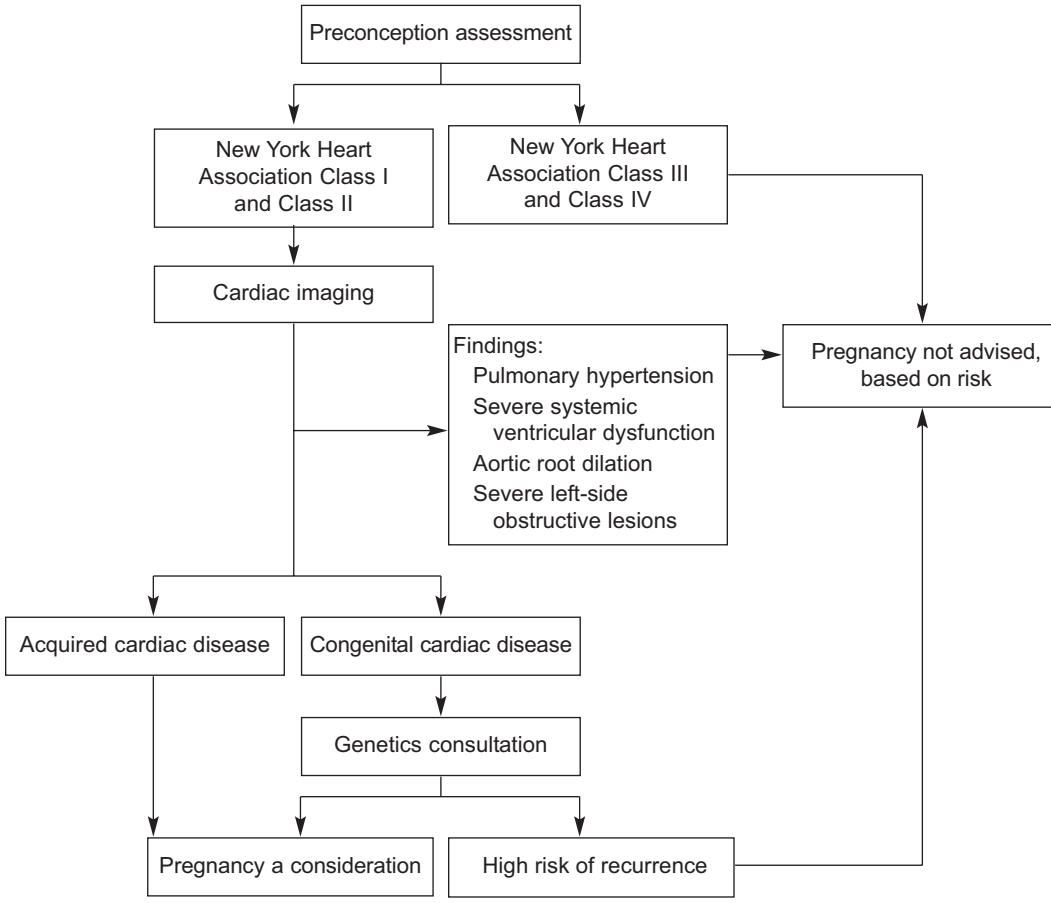

Fig. 1. Preconception assessment.
Simpson. Maternal Cardiac Disease Update. Obstet Gynecol 2012.

vides an opportunity to review available data that the patient needs to consider before embarking on what might be a very complicated and risky pregnancy. Although general preconception counseling will help the patient prepare for pregnancy, an individualized approach estimating the maternal and fetal risks related to her specific cardiac condition can help guide her decision-making (Fig. 1). An assessment of the patient's clinical status and ventricular function are necessary to best predict the outcome for pregnancy.

The New York Heart Association classification system remains the standard tool to describe a patient's functional status[7]:

- New York Heart Association class I: asymptomatic
- New York Heart Association class II: symptoms with greater than normal activity
- New York Heart Association class III: symptoms with normal activity
- New York Heart Association class IV: symptoms at bed rest.

Most women with functional class I or II tolerate pregnancy well and can expect a favorable outcome. In contrast, pregnancy is not advised for New York Heart Association class III or IV because everyday symptoms before pregnancy predict a poor prognosis.[8,9] Pregnancy is also contraindicated in women with certain cardiac conditions regardless of functional class because the maternal risk of death is so high (25–50%)[5]:

- pulmonary hypertension
- severe systemic ventricular dysfunction
- aortic root dilation (more than 4 cm)
- severe left-sided obstructive lesions

In women without a clear contraindication to pregnancy, an objective assessment of cardiovascular status should be completed before conception. In addition to the standard electrocardiogram, this may include an echocardiogram, stress testing, magnetic resonance imaging, and, in some cases, cardiac cath-

eterization. Exercise testing may identify patients who have more significant functional limitations than are elicited by history alone.[10] For example, asymptomatic women considering in vitro fertilization for age-related infertility may also have coexisting age-related heart disease. Although adverse cardiac events may affect any pregnant woman with heart disease, specific predictors of poor maternal outcome have been identified[8] (Table 1). Collaboration with an experienced cardiologist can help establish the best work-up for an individual patient as well as expand on the disease-specific risks of pregnancy, management options, and long-term prognosis.

In certain conditions such as severe left heart obstruction or significant right-to-left shunts, repair before pregnancy can improve outcomes. Consultation with cardiothoracic surgery or interventional cardiology can identify patients who would benefit from corrective surgery or percutaneous interventions such as balloon valvuloplasty, stent placements, and shunt closure in preparation for pregnancy. For instance, closure of a patent ductus arteriosus, atrial septal defect, or ventricular septal defect that has significant shunting in the nonpregnant state can decrease complications once the patient is pregnant. For a woman requiring a prepregnancy procedure or with major cardiac disease, consultation with an anesthesiologist specializing in obstetrics can help clarify anesthesia-related risks specific to pregnancy and her condition.

Table 1. Predictors of Major Cardiac Event in Pregnant Patients With Heart Disease*

Predictor	Odds Ratio (95% Confidence Interval)	*P*
Prior cardiac event or arrhythmia Heart failure Transient ischemic attack Stroke before pregnancy	6 (3–14)	<.001
New York Heart Association class greater than II or cyanosis	6 (2–22)	.009
Left heart obstruction Mitral valve area less than 2 cm^2 Aortic valve area less than 1.5 cm^2 Peak left ventricular outflow tract gradient greater than 30 mm Hg by echocardiography	6 (3–14)	<.001
Systemic ventricular dysfunction Ejection fraction less than 40%	11 (4–34)	<.001

* Major cardiac event=pulmonary edema, arrhythmia requiring treatment, stroke, cardiac arrest, cardiac death; 0 predictor=5% risk; one predictor=27% risk; two or more predictors=75% risk.

Data from Siu SC, Sermer M, Colman JM, Alvarez AN, Mercier LA, Morton BC, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation 2001;104:515–21.

Adverse perinatal outcomes, including miscarriage, fetal growth restriction, prematurity, and death, affect approximately 30% of pregnancies in patients with significant heart disease.[6,11] For women with congenital heart disease, there is also the risk of recurrence of cardiac anomalies in their offspring. Although the background risk for congenital heart defects is eight per 1,000 live births, the risk for children born to affected mothers is approximately 5%.[9,12] Disease-specific recurrence risks are available and consultation with a geneticist specializing in prenatal counseling and diagnosis can be particularly useful to patients with congenital heart defects or inherited conditions such as Marfan syndrome.

Health care practitioners providing care to reproductive-aged women, or older women contemplating pregnancy using assisted reproductive technologies, must consider the risks of known cardiac disease or the likelihood of unrecognized heart disease before conception. A multidisciplinary approach to preconception counseling is optimal for the patient with heart disease to determine whether acceptable outcomes can be expected and what management strategies may improve the prognosis.

Pregnancy Management

A multidisciplinary team is also a must in the ongoing care of pregnant patients with heart disease. These patients are at increased risk for complications including life-threatening events such as congestive heart failure, arrhythmias, and stroke, which require the expertise of experienced specialists for optimal antepartum, intrapartum, and postpartum management.

Hemodynamic Changes in Pregnancy

The ability of a cardiac patient to adapt to the physiological changes of pregnancy predicts the likelihood of a favorable outcome. Frequent office visits to assess functional status and serial evaluations of cardiac performance are necessary for the early recognition of complications. The expected increases in preload, cardiac output, and oxygen consumption coupled with the normal decrease in afterload in pregnancy may unmask or worsen cardiac disease in the pregnant woman.[13] In women without recognized heart disease, the diagnosis is often delayed because complaints of shortness of breath, decreased exercise tolerance, and peripheral edema are attributed to normal pregnancy. Echocardiography is the primary imaging modality used in pregnancy because both cardiac structure and function can be evaluated without risk to the patient or her developing fetus.

Table 2. Cardiovascular Changes With Pregnancy

Variable	First Trimester	Second Trimester	Third Trimester	Eight wk Postpartum
Heart rate (beats/min)	70±8	77±10	80±10	66±10
Cardiac output (L/min)	6.8±1.6	7.6±1.5	7.9±1.6	6.0±1.2
Stroke volume (mL)	95±20	99±20	99±19	87±17
Mean arterial pressure (mm Hg)	71±5	70±5	70±6	71±6
Left ventricle mass (g)	131±36	141±31	147±36	140±34

Data are mean±standard deviation.
Modified from Poppas A, Shroff SG, Korcarz CE, Hibbard JU, Berger DS, Lindheimer MD, et al. Serial assessment of the cardiovascular system in normal pregnancy. Role of arterial compliance and pulsatile arterial load. Circulation 1997;95:2407–15.

Although these cardiovascular changes are well tolerated in normal pregnancy, a patient with cardiac disease can deteriorate from a stable to critical condition as a result of the added demands on the heart over the course of gestation[13] (Table 2).

Physiological demands of normal peripartum events make this a critical time for patients with heart disease. During labor, the combination of pain, anxiety, and contractions results in further increases in maternal heart rate, stroke volume, cardiac output, and blood pressure. Supine positioning for cervical examinations or bladder catheterization can cause the gravid uterus to compress the inferior vena cava and decrease venous return. In a healthy woman, this may manifest as lightheadedness or fetal heart rate decelerations, but the effect may be more ominous for a cardiac patient who depends on a certain level of preload for normal functioning. The second stage of labor is a time of increased hemodynamic and oxidative cardiac stress.[13] For patients with limited cardiac reserve, the 500-mL autotransfusion that occurs after delivery of the placenta may not be tolerated.[12] As a result, immediate postpartum management warrants close observation for congestive heart failure and measurement of the patient's fluid balance and, in some cases, may require admission to an intensive care unit for telemetry or more invasive monitoring and therapy. Although left ventricular systolic function returns to baseline values within a couple weeks of delivery, the physiological left ventricular hypertrophy and its associated diastolic dysfunction may be slower to normalize postpartum.[14] Close surveillance of cardiac patients after birth is necessary because the early postpartum period is often a time of acute decompensation.

Anticoagulation

Despite potential maternal and fetal complications, anticoagulation may be recommended in certain cardiac conditions such as mechanical heart valves, atrial fibrillation, and pulmonary hypertension. Decisions about the therapeutic approach should be made in consultation with cardiology and hematology, but all experts agree that unadjusted prophylactic regimens are insufficient for patients with mechanical heart valves.[15,16] Although bioprosthetic valves are preferred for women of reproductive age who are considering childbearing, mechanical heart valves may be placed as a result of their greater durability. Mechanical valves have significant sheer effects on circulating blood, which can result in platelet activation and thrombus formation. Although bioprosthetic valves require no anticoagulant therapy, full anticoagulation is warranted for patients with mechanical valves.[15]

Warfarin is the standard therapeutic choice in nonpregnant patients, but it has the potential for fetal embryopathy when used during the period of organogenesis and for fetal intracerebral hemorrhage when used later in gestation. The risk of embryopathy seems to be low with daily warfarin doses 5 mg or less, but intracerebral bleeding has been observed at lower doses.[17,18] Unfractionated and low-molecular-weight heparins do not cross the placenta so fetal risks are reduced; however, the frequency of valve thrombosis seems to be higher when heparins are used in pregnancy.[15,19] Although maternal hemorrhagic complications can occur irrespective of the anticoagulant used, heparins offer the advantage of a short half-life, which may permit the use of regional anesthesia when a scheduled delivery is possible. There also appears to be a higher frequency of stillbirth in these patients regardless of the type of anticoagulation used.[20] At the present time, there is no consensus on the optimal regimen for anticoagulation in pregnancy, but three main approaches have been suggested for women with mechanical heart valves[15] (Table 3). Although most regimens include subcutaneous heparins, in patients who refuse twice-daily injections or are more likely to develop a thrombus, oral anticoagulation with warfarin may be necessary throughout pregnancy.[20]

Table 3. Options for Anticoagulation With Mechanical Heart Valves in Pregnancy

Drug Regimens	Monitoring Test	Target Goal
Adjusted-dose, twice-daily unfractionated heparin throughout pregnancy	Activated partial thromboplastin time	2 times control, 6 h after injection
Adjusted-dose, twice-daily low-molecular-weight heparin throughout pregnancy	Antifactor Xa level	1.0–1.2 units/mL, 4–6 h after injection
Adjusted-dose, twice-daily unfractionated or low-molecular-weight heparin in first trimester and again at 35–36 wk, changing to adjusted-dose, once-daily warfarin in the middle of pregnancy	Same as above for heparins; international normalized ratio for warfarin	Same as above for heparins; international normalized ratio of 3.0 (range 2.5–3.5) for warfarin

Data from Bates SM, Greer IA, Hirsh J, Ginsberg JS. Use of antithrombotic agents during pregnancy: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126(suppl):627S–44S.

When timed deliveries are possible, anticoagulation can be managed to permit epidural placement for a trial of labor or cesarean delivery.[21] This requires coordination with anesthesiology and nursing to have procedures done during periods of normal hemostasis. Intravenous unfractionated heparin is the agent of choice during the intrapartum period because it can be easily adjusted and discontinued 4–6 hours before regional anesthesia and delivery to minimize maternal risks of spinal hematoma and obstetric hemorrhage.[15] In the absence of any contraindication, intravenous heparin then can be restarted postpartum, 6–12 hours after a vaginal delivery and 12–24 hours after a cesarean delivery. Warfarin is usually started the night after delivery provided there are no bleeding complications and heparin is continued until an international normalized ratio of 2 or greater is achieved.[15]

Endocarditis Prophylaxis

Infective endocarditis prophylaxis is no longer recommended for vaginal or cesarean deliveries in the absence of infection irrespective of the type of maternal heart disease.[22] The current recommendation from the American Heart Association is that only when deliveries are associated with infection should patients with high-risk cardiac lesions receive intrapartum prophylaxis[22,23] (Box 1). Maternal congenital heart disease is not an automatic indication for routine endocarditis prophylaxis but when indicated, one of the following is an acceptable option preferably given 30–60 minutes before delivery:

- 2 g ampicillin intravenously
- 1 g cefazolin intravenously
- 1 g ceftriaxone intravenously (±1 g vancomycin intravenously if *Enterococcus* infection is a concern)
- 600 mg clindamycin intravenously (±1 g vancomycin intravenously if *Enterococcus* infection is a concern)

Box 1. Indications for Intrapartum Endocarditis Prophylaxis

Anticipated vaginal or cesarean delivery associated with infection AND

1. Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
2. Previous infective endocarditis
3. Congenital heart disease that meets one of the following conditions:
   a. Unrepaired cyanotic defect including palliative shunts and conduits
   b. Completely repaired defects with prosthetic material or device whether placed by surgery of catheter intervention during the first 6 months after the procedure
   c. Repaired defect with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device

Modified from Antibiotic prophylaxis for infective endocarditis. ACOG Committee Opinion No. 421. American College of Obstetricians and Gynecologists. Obstet Gynecol 2008;112:1193–4.

Patients with complete repairs that require the use of prosthetic materials or devices also do not need prophylaxis beyond 6 months postprocedure because endothelialization of the prosthetic materials should be complete by that time.[23] In clinical practice, antibiotics for endocarditis prophylaxis are often used more than advised by the American Heart Association, in part because intrapartum infection can be difficult to confirm and timing of delivery is difficult to predict. In addition, some consultants in cardiology

and cardiothoracic surgery may still recommend endocarditis prophylaxis for certain patients during the intrapartum period. However, only women with high-risk cardiac conditions are currently candidates for endocarditis prophylaxis and only when delivery is complicated by infection.

Intrapartum Care

An individualized approach, with input from the multidisciplinary team, is recommended for the intrapartum management of women with heart disease. The majority of patients can safely undergo a trial of labor and experience a vaginal birth.[9] In certain circumstances, an operative vaginal delivery may be performed to limit the stress associated with pushing in the second stage of labor. Early epidural placement can decrease the sympathetic stimulation and myocardial oxygen consumption associated with labor and is recommended for most women with heart disease.[24] In patients with fixed cardiac output, the initiation of epidural analgesia must be done slowly with careful attention to fluid balance and clinical status. There is a lack of consensus regarding the use of invasive monitoring during labor and delivery. Although many centers have decreased the use of pulmonary artery catheters, peripheral arterial lines and central venous lines are often used to assess a patient's cardiovascular status during the peripartum period. In general, cesarean delivery is reserved for normal obstetric indications and, when required, regional anesthesia is preferred.[25] Although spinal anesthesia may be used in well-compensated, stable patients, epidural anesthesia is associated with fewer hemodynamic changes and, therefore, the approach of choice in most cases.[24] Despite the increased risks of hemorrhage, infection, and large fluid shifts, there are a few conditions in which labor is ill-advised and cesarean delivery is recommended:

- dilated aortic root (more than 4 cm) or aortic aneurysm
- acute severe congestive heart failure
- a history of recent myocardial infarction
- severe symptomatic aortic stenosis
- warfarin administration within 2 weeks of delivery
- need for emergency valve replacement immediately after delivery

At one end of the spectrum, a woman with heart disease can have an easy, uncomplicated pregnancy; at the other end, pregnancy can result in her death and the death of her child. No simple algorithm can be applied to the diverse cardiac conditions seen in pregnancy and be expected to eliminate all adverse maternal and perinatal events. However, both general and disease-specific strategies can help to optimize care in preparation for, during, and after pregnancy.

Special Considerations for Specific Cardiac Conditions

Heart disease represents a heterogeneous group of conditions, each with distinctive features, different management tactics, and specific pregnancy-related risks. In some cases, lesions are grouped together because the management and expected prognoses are similar. For example, regurgitant valvular lesions are usually well tolerated and associated with favorable maternal and fetal outcomes. Conversely, certain cardiac conditions warrant special consideration as a result of the risky nature of pregnancy for affected patients: pulmonary hypertension, dilated aortopathy, cardiomyopathy, ischemic heart disease, left-sided obstructive lesions, and congenital heart disease.

Pulmonary Hypertension

Although pregnancy is contraindicated in cases of pulmonary hypertension, some patients are diagnosed late or refuse termination earlier in gestation, challenging the medical team to do what they can to optimize outcome. Pulmonary hypertension is defined as a systolic pulmonary artery pressure more than 30 mm Hg or a mean pulmonary artery pressure of more than 25 mm Hg and can be primary or secondary.[26] In cases secondary to congenital heart disease, reversal of flow through left-to-right shunts can occur resulting in the development of Eisenmenger's syndrome. The most common cause of Eisenmenger's syndrome is a large ventricular septal defect, which, over time, results in increased pulmonary vascular blood flow and increased pulmonary resistance that eventually exceeds systemic vascular resistance so that right-to-left shunting occurs with marked cyanosis. Once cyanosis has developed, surgical correction of the shunt no longer improves long-term prognosis. Primary, secondary, and pulmonary hypertension related to congenital heart disease all have significant risks of maternal death, although the risks seem to be trending downward[27,28] (Table 4).

Medical therapy for ongoing pregnancies with pulmonary hypertension is focused on avoiding further increases in pulmonary vascular resistance and maintaining right ventricular preload and ventricular contractility. Calcium antagonists, inotropic agents, diuretics, and supplemental oxygen are routinely used in the treatment of pulmonary hypertension.[26] Angiotensin-converting enzyme inhibitors are contra-

Table 4. Comparison of Maternal Mortality in Pulmonary Hypertension Between 1978–1996 and 1997–2007 (P=.047)

Cases of Pulmonary Hypertension	n	Maternal Mortality 1978–1996 (%)	n	Maternal Mortality 1997–2007 (%)
Primary	27	30	29	17
Secondary	25	56	15	33
Associated with congenital heart disease*	73	36	29	28

* Includes cases with Eisenmenger syndrome.

Data from Bédard E, Dimopoulos K, Gatzoulis MA. Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? Eur Heart J 2009;30:256–5; and Weiss BM, Zemp L, Seifert B, Hess OM. Outcome of pulmonary vascular disease in pregnancy: a systemic overview from 1978 through 1996. J Am Coll Cardiol 1998;31:1650–7.

indicated in pregnancy but may be considered after delivery. Anticoagulation is recommended as a result of the risk of pulmonary arterial thrombosis.[26] Inhaled nitric oxide causes selective vasodilation of the pulmonary vascular bed and has been used successfully in pregnancy.[26] Newer agents such as intravenous epoprostenol and aerosolized iloprost have also been observed to reduce pulmonary vascular resistance in these patients and may improve survival.[29,30] Despite advances in medical therapy and improvements in peripartum management, current mortality rates are still unacceptably high, which warrant advice against pregnancy.[28] Perinatal risks are also high in ongoing pregnancies with spontaneous loss, poor fetal growth, and complications of prematurity affecting up to 30% of cases.[26,28]

Dilated Aortopathy

The majority of women with significant aortic root dilation during pregnancy have Marfan syndrome, an autosomal-dominant connective tissue disorder associated with regurgitant valvular disease and cystic medial degeneration of the aorta resulting from mutations in the fibrillin gene on chromosome 15q21.[31] Given that there is a 50% risk of Marfan syndrome in the offspring, patients should be offered genetic counseling before conception and prenatal diagnosis in early pregnancy. Many experts counsel women with Marfan syndrome against pregnancy as a result of the potential for serious cardiovascular complications, but not all patients heed this warning.[32] The greatest risk in Marfan syndrome is aortic dissection or rupture[5,33] (Table 5). For nonpregnant patients who are symptomatic or have an aortic root dimension of 5.0 cm or greater or a rapidly dilating aorta at a rate of 0.5 cm or greater per year, surgical repair is recommended.[32,34] Pregnancy seems to accelerate the pathologic changes in the aorta, perhaps in response to hormonal and hemodynamic influences. Women with aortic roots less than 4 cm tend to tolerate pregnancy well but aortic dissection remains a risk even below this cutoff.[5] A high level of suspicion is warranted when a patient with Marfan syndrome presents with chest or back pain and urgent computed tomography or magnetic resonance imaging should be obtained to exclude the diagnosis of aortic dissection.

Prophylactic β-blockade has become the standard medical approach for pregnant women with Marfan syndrome because it reduces hemodynamic stress on the ascending aorta and slows the rate of dilation. Without routine β-blockade, aortic complications including dilation and dissection increase fivefold in pregnancy.[35] Serial maternal echocardiograms are recommended throughout gestation to help the multidisciplinary team determine the safest management plan. Vaginal delivery with regional analgesia and an assisted second stage seems safe for women with an aortic root diameter less than 4 cm. When the aortic root measures 4 cm or greater, elective cesarean delivery is recommended with consideration of postpartum replacement of the proximal aorta, but advice varies with 4–4.9 cm dilation.[9] Based on the progressive nature of the disease and potential for complications such as aneurysmal dilation and dissection even after aortic repair, elective delays in childbearing should be avoided. Overall, the maternal mortality associated with Marfan syndrome is approximately 1% but increases to more than 20% in cases of aortic dissection.[27,36]

Table 5. Risk of Dissection or Rupture Based on Aortic Root Size

Aortic Root Diameter (cm)	Risk of Dissection or Rupture
Less than 4	1% during pregnancy
4 or more	10% during pregnancy
4.0–4.9	2% yearly rate
5.0–5.9	3% yearly rate
6 or more	7% yearly rate

Data from Elefteriades JA. Indications for aortic replacement. J Thorac Cardiovasc Surg 2010;140(suppl):S5–9; discussion S45–51.

In addition to Marfan syndrome, aortic dissection or rupture can complicate pregnancies in women with bicuspid aortic valve, chronic hypertension, coarctation, and a number of genetic conditions such as Ehlers-Danlos syndrome, Loeys-Dietz syndrome, and Turner syndrome.[37] Although information on outcomes in non-Marfan cases is limited, pregnancy is not advised in any patient if aortic root dilation or aneurysmal formation is detected before conception. In most cases, similar criteria for prophylactic aortic root replacement are used if such a woman is contemplating pregnancy.[9,37] One exception is Loeys-Dietz syndrome, an autosomal-dominant condition associated with aortic aneurysmal formation and rupture at smaller diameters than in Marfan syndrome.[38,39] Aortic dissection without dilation has also been reported in Ehlers-Danlos syndrome type IV, another autosomally inherited connective tissue disorder.[40,41] The management of patients with these syndromes is less clear because the risk of aortic dissection is less predictable and multiple other vessels can be involved. Women with aortic dilation from atypical causes may not seek preconception counseling and, thus, present in pregnancy with unexpected and potentially life-threatening risks.

Cardiomyopathy

Cardiomyopathies can be classified broadly into two groups: peripartum and nonperipartum. Patients with hypertrophic, dilated, or restrictive cardiomyopathies are often aware of their diagnosis before pregnancy compared with peripartum cardiomyopathy that develops de novo in the weeks before and months after delivery.

The most common complication for pregnant patients with pre-existing cardiomyopathies or with new-onset peripartum cardiomyopathy is heart failure. With the exception of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers that are contraindicated as a result of risks of fetal renal injury, the medical treatment of heart failure is the same regardless of the underlying cause and includes oxygen, diuretics, β-blockers, vasodilators, and inotropes such as digoxin.[42] Anticoagulation is also indicated as a result of the risk of thromboembolism, particularly in patients with poor systolic function, atrial fibrillation, or a mural thrombus. Critically ill patients may be candidates for intra-aortic balloon pump counterpulsation, extracorporeal membrane oxygenation, or placement of a left ventricular assist device after delivery as a bridge to transplantation.[43] Maternal death can be the result of chronic progressive congestive heart failure, fatal arrhythmias, or thromboembolic complications.

Nonperipartum Cardiomyopathy

Young women with hypertrophy cardiomyopathy tend to be asymptomatic and tolerate pregnancy well. Although familial and sporadic cases have been reported, this is an autosomal-dominant disease with a 50% recurrence risk in the offspring.[44] Asymmetric hypertrophy of the left ventricle is the classic feature of this condition, which results in diastolic dysfunction as a result of impaired relaxation of the ventricle. In approximately 20% of cases, left ventricular outflow obstruction occurs with the potential for complications similar to aortic stenosis.[45] At gradients greater than 30 mm Hg, patients become symptomatic and beyond 100 mm Hg, there is a significant risk of deterioration from heart failure, atrial and ventricular arrhythmias, embolic stroke, and sudden death.[42,46] Pregnancy is not advised when severe left-sided obstruction is detected before pregnancy.

Dilated cardiomyopathy can be the result of myocarditis, ischemic heart disease, hypertensive disorders, alcohol abuse, and medication toxicity but in one third of cases, the condition is familial with autosomal-dominant inheritance, and in 50% of cases, no cause is found.[44] Although etiology-specific risks are not well established, women with left ventricular dysfunction and an ejection fraction less than 40% are at high risk for adverse maternal and perinatal events.[42] In general, women with dilated cardiomyopathy are advised against pregnancy.

Restrictive cardiomyopathy is a rare, inherited form of heart disease that carries a poor prognosis.[44] Similar to patients with other cardiomyopathies, women with restrictive cardiomyopathy have limited cardiovascular reserve increasing the risk for overt heart failure, dysrhythmias, and death in pregnancy.[42]

Peripartum Cardiomyopathy

Although peripartum cardiomyopathy comprises less than 1% of cardiac events in pregnancy, it accounts for an increasing number of pregnancy-related deaths.[3,5] The diagnosis is based on the following:

- cardiac failure in the last month of pregnancy or within 5 months postpartum
- no other identifiable cause of heart failure
- absence of heart disease before the last month of pregnancy
- left ventricular systolic dysfunction (left ventricular ejection fraction less than 45%)

The majority of cases present postpartum, 75% in the first month, with only 10% diagnosed before delivery.[47] Various risk factors for peripartum cardiomy-

opathy are recognized including maternal age older than 30 years, obesity, chronic hypertension, multiparity, multiple gestation, tocolysis with β-agonists, preeclampsia, low socioeconomic status, and African American race.[48] However, the exact etiology of peripartum cardiomyopathy remains a mystery. Myocarditis, autoimmune reactions, stress-activated cytokines, accelerated myocyte apoptosis, and prolactin cleavage products have all been implicated, but no clear causative links have been found. Endomyocardial biopsy is no longer routinely recommended in peripartum cardiomyopathy.

Mortality rates for peripartum cardiomyopathy have been reported to be as high as 25–50% with the majority of deaths occurring within a few months of delivery.[7] Overall, 30–50% of patients recover fully, but recent reports suggest the recovery phase may be considerably longer than the expected 6 months.[49] Cardiac transplantation is eventually necessary in 10% of cases.[47] Poor prognostic features for subsequent pregnancy include a large left ventricular end-diastolic dimension at the time of diagnosis, left ventricular ejection fraction less than 30% on initial testing, and a failure of left ventricular function to normalize by 6 months.[50] The 35% risk of recurrence is reported to be lower in women with complete return to baseline function and normal stress testing.[49,50] Despite recent studies reporting a lower maternal mortality rate, subsequent pregnancies in these patients are risky and should be discouraged[50,51] (Table 6).

Ischemic Heart Disease

Although ischemic heart disease is relatively rare in pregnancy, it has contributed to the rise in maternal cardiac deaths in developed countries.[16,52] Pregnancy increases the overall probability of myocardial infarction by twofold to fourfold, and in the first few days postpartum, this escalates to a sixfold risk compared with age-matched nonpregnant women.[53] The likelihood of myocardial infarction is greatest in pregnant women older than age 40, who have a 30-fold higher risk compared with gravid women younger than 20 years of age in a control group.[54] Acute myocardial events have also been reported in older women who have undergone in vitro fertilization to achieve pregnancy.[55] Pre-existing ischemic heart disease is more likely with advancing age, but other additional risk factors such as obesity, diabetes, and hypertension are increasing at every age.[56] Careful screening and evaluation of women at highest risk for atherosclerosis is warranted because this is the leading cause of acute myocardial syndrome in pregnancy. Stress echocardiography can be useful to identify ischemia and ventricular dysfunction in patients at risk.[57]

The initial signs and symptoms of cardiac ischemia are often attributed to the normal physiological changes of pregnancy, which delay the diagnosis and opportunity for acute management measures. Characteristic changes in the electrocardiogram and cardiac enzymes are diagnostic, but creatine kinase and its MB fraction are affected by labor, increasing twofold after delivery, so troponins are followed serially during the peripartum period because their levels are less influenced by intrapartum events.[56] Morphine, nitrates, β-blockers, calcium channel blockers, and low-dose aspirin can all be used in the treatment of ischemic heart disease, but angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists are not advised until postpartum. As a result of limited data on their safety in pregnancy, the use of aldosterone antagonists and statins is also not recommended. Cardiac catheterization and interventional cardiac procedures with shielding expose the developing fetus to less than 1 Rad of radiation and are considered safe in pregnancy.[56] Percutaneous coronary angioplasty, with or without stenting, is now performed in more than 40% of cases and is associated with improved pregnancy outcomes.[56] Percutaneous coronary intervention, using angioplasty or the placement of bare metal stents, is now the procedure of choice when revascularization is necessary during pregnancy. This approach avoids drug-eluting stents that have a higher risk of thrombosis and open heart surgery for coronary artery bypass, which has a 30% fetal loss rate.[56] Although thrombolysis has been used in pregnancy, it should only be considered when

Table 6. Outcome of Subsequent Pregnancies After Peripartum Cardiomyopathy

History of Peripartum Cardiomyopathy	n	Congestive Heart Failure (%)	Maternal Mortality (%)	Preterm Delivery (%)
Normalization of left ventricle function	28	21	0	11
Nonnormalization of left ventricle function	16	44	19	37

Data from Elkayam U, Tummala PP, Rao K, Akhter MW, Karaalp IS, Wani OR, et al. Maternal and fetal outcomes of subsequent pregnancies in women with peripartum cardiomyopathy. N Engl J Med 2001;344:1567–71.

percutaneous coronary treatments are not available because of the potential maternal and fetal risks.

Overall myocardial infarction has a maternal mortality rate of 10–20% with the majority of deaths occurring postpartum, at the time of infarction or within the first 2 weeks, and in multigravida women 34 years of age or older.[56,58,59] Most fetal deaths are secondary to maternal death.[56] Subsequent pregnancies are not advised after surviving a myocardial infarction but may be considered in select women with adequate ventricular performance and normal coronary arteries. Interestingly, at least 20% of women who experience a myocardial infarction in pregnancy have normal coronary arteries by angiography.[59] In addition to atherosclerosis, coronary artery spasm, thromboembolism, and coronary artery dissection have all been associated with ischemic heart disease in pregnancy.[56,59]

Left-Sided Obstructive Lesions

Aortic Stenosis

Conditions such as aortic stenosis or hypertrophic cardiomyopathy can lead to obstruction of output from the systemic left ventricle with devastating consequences. Valvular aortic stenosis can be acquired, most often related to rheumatic heart disease, or congenital as a primary lesion or secondary to a bicuspid valve. Bicuspid aortic valve is the cause of most aortic stenosis in developed countries affecting 1–2% of the population with a male predominance of 4:1.[37] Valvular stenosis in this population often progresses slowly with age and may escape diagnosis until later in life. Asymptomatic women with unremarkable resting electrocardiograms, normal exercise test, good left ventricular function, and prepregnancy aortic valve peak pressure drop of less than 80 mm Hg measured by Doppler echocardiography can expect a favorable pregnancy outcome.[5] Affected individuals are generally asymptomatic until the valve area decreases to less than one third of its original size or less than 1 cm^2.[37] Although mild aortic stenosis is well tolerated, patients with severe aortic stenosis are at risk for angina, myocardial infarction, syncope, and sudden death.

Maintaining adequate cardiac output across a constricted aortic valve can be challenging during pregnancy. Longstanding obstruction of outflow results in left ventricular hypertrophy, diastolic dysfunction, and eventually a fixed cardiac output. The inability to increase output in response to increases in preload and heart rate can be life-threatening because the fixed flow can compromise coronary and carotid artery perfusion. Bed rest and β-blockers are used to decrease heart rate, which increases the time for left ventricular ejection and coronary filling. The demands of labor and volume shifts associated with delivery are significant stressors to patients with fixed cardiac outputs and management of anesthesia is critical during this time. Hypovolemia is not well tolerated so maintaining a positive fluid balance is recommended.[7] Although some patients may develop overt heart failure and atrial arrhythmias, most tolerate mild degrees of pulmonary edema. Overall, 10% of women with congenital aortic stenosis experience cardiac complications during pregnancy.[12] The fixed cardiac output can also compromise uteroplacental perfusion and fetal growth in these pregnancies.

Severe aortic stenosis, defined as a peak gradient of more than 50 mm Hg, warrants repair and elective repair should be considered in women with gradients 30 mm Hg or greater or left ventricular ejection fractions less than 30% who are contemplating childbearing.[60,61] Pregnant women tolerate cardiopulmonary bypass and open valve replacement nearly as well as nonpregnant women except when it is emergently needed.[61] The risk of fetal death with cardiopulmonary bypass is more than 20% regardless of the urgency so when possible, valve replacement is delayed until after delivery.[61] In the absence of significant aortic regurgitation, balloon valvuloplasty can be considered in cases of severe aortic stenosis that require intervention before delivery. Although this temporary measure may be used early in pregnancy, preterm delivery and postpartum repair is often the preferred approach in cases of critical aortic stenosis beyond 28–32 weeks of gestation.

Mitral Stenosis

Although mitral stenosis may occur in complex congenital heart defects, it tends to be an acquired valvular lesion in adults, resulting from rheumatic heart disease. Affected women often present with pulmonary edema or atrial fibrillation toward the end of the second and beginning of the third trimester and recent immigrants are at increased risk.[16] Restricted physical activity, diuretics, and β-blockers for rate control are the mainstays of medical management. Mitral valve commissurotomy, balloon valvuloplasty, or valve replacement are recommended before pregnancy if the valve area is less than 1.2 cm^2 or the woman is symptomatic.[62] Balloon mitral valvuloplasty has been successfully used during pregnancy in women with heart failure who are refractory to medical therapy.[9] Cardiac surgery is reserved for extreme emergencies in pregnancy as a result of the high risk of fetal death, particularly if done in the first trimester.

High-flow, high-pressure, normothermic bypass is the safest for the fetus and hyperoxygenation with maternal hematocrit more than 25% should be maintained throughout the procedure.[62] Fetal heart and uterine monitoring are recommended to aid the multidisciplinary team in taking actions to maximize placental perfusion during open heart surgery. Depending on the level of nursery and capabilities of the institution, delivery of a preterm neonate followed by valve replacement for the mother may be the best approach after 28–32 weeks. Overall, maternal mortality with mitral valvular stenosis is approximately 5%, with a perinatal mortality rate of 10–30%.[62]

Congenital Heart Disease

Advances in surgical techniques and medical therapies for congenital heart disease have resulted in an increasing number of patients reaching reproductive age who are interested in pregnancy. Today approximately 85% of children born with structural heart defects are expected to survive to adulthood and currently, congenital heart disease comprises more than 50% of all cardiac disease observed in pregnancy.[1,63] Despite the recent rise in cases reaching childbearing age, there has been a corresponding decline in maternal mortality from congenital heart disease, which, in part, is attributed to improvements in multidisciplinary cardiac care.

Women with congenital heart disease are at risk of cardiac complications in pregnancy but these risks vary depending on the lesion and functional status[12,64] (Table 7). The hemodynamic changes of pregnancy can unmask or overwhelm a previously well-compensated defect. Significant arrhythmias, heart failure, myocardial infarction, stroke, and death are more common during pregnancy in women with congenital heart disease than in the general population.[11] The most prevalent cardiac complications are arrhythmias, affecting 5% of patients, and heart failure, in 1–2% of patients.[65] The management of arrhythmias does not differ significantly between pregnant and nonpregnant patients and electrical cardioversion is safe during pregnancy.[60] Factors associated with maternal cardiac complications include the presence of cyanotic heart disease, use of cardiac medications before pregnancy, left heart obstruction, presence of a mechanical valve, and significant atrioventricular regurgitation related to complex defects.[65] Exercise testing and heart rate response before conception can help predict clinical outcomes and the risk of maternal mortality in congenital heart disease.[10] Adverse neonatal outcomes such as small for gestational age, prematurity, and death are observed in 20–30% of cases with a recurrence of congenital heart disease in 5–7% of live offspring.[64,65] Women with congenital heart disease are also at risk for late cardiac events beyond 6 months postpartum.[66] Late events affect more than 10% of women, particularly those with low functional status, cyanosis, ventricular dysfunction, left heart obstruction, and a history of prior cardiac complications.[66]

A comprehensive review of the spectrum of congenital heart defects and lesion-specific management during pregnancy is beyond the scope of this article. In general, women with congenital heart disease who are asymptomatic during activities of daily

Table 7. Congenital Heart Disease: Estimated Risk of Cardiac Complications in Pregnancy

High Risk of Complications or Death	Moderate Risk of Complications (5–15%)	Low Risk of Complications (Less Than 1%)
Left-to-right shunt with pulmonary hypertension	Mild-to-moderate aortic stenosis	Isolated atrial septal defect, repaired or unrepaired
Reversal of shunt with Eisenmenger's syndrome	Marfan syndrome with normal aorta	Isolated ventricular septal defect, repaired or unrepaired
Marfan syndrome with aortic root dilation	Unrepaired cyanotic defects such as tetralogy of Fallot	Pulmonic or tricuspid valve disease
Coarctation of aorta, uncorrected with proximal aortic dilation	Systemic right ventricle such as complete and congenitally corrected transposition of great arteries	Coarctation, repaired with normal proximal aortic size
Severe symptomatic left-sided obstructive lesions such as aortic stenosis, hypertrophic cardiomyopathy	Well-functioning Fontan palliation for hypoplastic ventricles, complex defects Palliated tetralogy of Fallot with severe pulmonic regurgitation and right ventricular dysfunction	Repaired tetralogy of Fallot with normal right ventricular function and competent pulmonic valve

Modified with permission from Elsevier from Harris IS. Management of pregnancy in patients with congenital heart disease. Prog Cardiovasc Dis 2011;53:305–11; and Hung L, Rahimtoola SH. Prosthetic heart valves and pregnancy. Circulation 2003;107:1240–6.

living tolerate pregnancy well. Subsets of women who have survived surgery for complex cardiac defects deserve special mention because they often reach their reproductive years in good health and are interested in childbearing.

Postrepair of Tetralogy of Fallot

Tetralogy of Fallot is the most common form of cyanotic cardiac lesion and long-term survival is rare without surgical correction. This lesion consists of severe pulmonary stenosis, a large ventricular septal defect, right ventricular hypertrophy, and an overriding aorta. Overall, 15% of cases have 22q11 deletion syndrome, a condition with a wide spectrum of clinical features, which may affect prognosis and warrants genetic counseling to discuss the risk of recurrence.[67] Pregnancy with uncorrected tetralogy of Fallot is not advised because the maternal mortality rate is as high as 15% with a 30% fetal loss rate.[68] Although palliative procedures were done in the past, most patients with tetralogy of Fallot now have surgical correction of the defect, which involves patching the ventricular septal defect and enlarging the right ventricular infundibulum. Ectopic ventricular contractions are common after complete repair, and ventricular tachyarrhythmias, syncope, and sudden death are late complications in 1–3% of patients.[37,68] Residual pulmonary regurgitation, right ventricular outflow obstruction, and right ventricular dilation and dysfunction with tricuspid regurgitation may also follow successful repairs.[37] Left ventricular dysfunction may be present from previous volume overload, thus increasing the likelihood of complications during pregnancy.

In general, favorable pregnancy outcomes are expected in asymptomatic patients postrepair of tetralogy of Fallot in the absence of significant valvular regurgitation, right ventricular obstruction, or dysfunction.[12,69] Overall, 7–8% of women experience cardiac complications such as supraventricular arrhythmias and right heart failure but maternal death is rare.[68,70] As a result of risks of deterioration and adverse outcomes, patients with severe pulmonary regurgitation or right ventricular systolic dysfunction postrepair should avoid pregnancy.

Postatrial Switch Repair of Complete Transposition of the Great Arteries

In complete transposition of the great arteries, the aorta arises from the right ventricle and the pulmonary artery arises from the left ventricle so early survival is dependent on the presence of additional lesions to allow for the mixing of venous and arterial blood. A large ventricular septal defect may provide a natural shunt, or an urgent balloon atrial septostomy may be needed in the newborn period. In the past, complete transposition was managed with an interatrial repair such as the Mustard or Senning procedure, which redirects systemic venous return to the left ventricle and pulmonary venous return to the right ventricle.[71] With these palliative procedures, the morphologic right ventricle supports the systemic circulation, which increases the risk of systolic dysfunction during pregnancy.

Although most women postatrial switch repairs have favorable pregnancy outcomes, significant arrhythmias, heart failure, and death have been reported.[72,73] Supraventricular tachyarrhythmias are common after atrial switch procedures, affecting more than 20% of patients, and women with this history are at highest risk of atrial arrhythmias during pregnancy.[68,71] Even asymptomatic women with good functional status may experience heart failure if their systemic right ventricle falters in response to the volume loading of normal pregnancy. Overall, a deterioration of functional class occurs in one third of patients during pregnancy and can last beyond 1 year in up to 10% of cases.[73] Given these risks and up to a 10% perinatal mortality rate, pregnancy after atrial repair should only be undertaken with considerable caution.[73]

Postarterial Switch Repair of Complete Transposition of the Great Arteries

The arterial switch, or Jatene operation, has become the standard surgical approach for complete transposition of the great arteries. This anatomic repair establishes the left ventricle as the systemic ventricle, a significant advantage over the atrial palliative procedures. The 15-year survival rate for patients undergoing the arterial switch operation is more than 85%.[74] The early survivors of this procedure are now adults but pregnancy-related data are scant. Although fewer complications are anticipated with the arterial switch operation, aortic valve dysfunction, coronary artery obstruction, and right ventricular outflow obstruction have been observed.[12,72] The development of tachyarrhythmias with impaired systolic function seems to be a common cardiac complication in pregnancy.[75] However, favorable outcomes are expected in asymptomatic patients.

Post-Fontan Palliation

The Fontan procedure is a palliative measure for a broad range of anatomic abnormalities that lack suitability for a two-ventricle repair. In cases of single-ventricle physiology, the ventricle is chronically overloaded and at risk for failure. The basic Fontan

procedure results in systemic venous blood bypassing the single ventricle and directly entering the pulmonary artery.[71] Although this reduces volume load to the single ventricle, it causes elevated systemic venous and right atrial pressures, which places the patient at risk for peripheral edema, ascites, and arrhythmias. Various modifications of the procedure have led to progressive improvements in outcomes with the 10-year survival rate after Fontan palliation now reaching more than 85%.[71]

Patients with single ventricles have limited ability to increase cardiac output and may not tolerate the hemodynamic changes of pregnancy. Although pregnancy poses significant risks, successful pregnancies after Fontan repair have been reported.[76] However, women are at risk for systemic venous congestion, atrial flutter and fibrillation, deterioration of ventricular function, and preterm birth.[71,77] The process of pregnancy and delivery may also have a harmful effect on long-term cardiovascular function in women who have undergone a Fontan repair.[78] Although pregnancy is tolerated in asymptomatic patients with good ventricular function, no pulmonary hypertension, and oxygen saturation greater than 85%, there is still up to a 2% risk of maternal death.[9] Until further data become available, caution is advised regarding childbearing in women post-Fontan repair.

SUMMARY

The complexity of cardiac disease observed in pregnant women is changing:

- Cardiac disease is now the leading cause of indirect maternal mortality.
- Congenital heart disease comprises more than 50% of cardiac disease seen in pregnancy.
- Ischemic heart disease is on the rise as a result of delayed childbearing, obesity, hypertension, and diabetes.
- Pregnancy is contraindicated in women with pulmonary hypertension of any etiology, severe systemic ventricular dysfunction, dilated aortopathy, and severe left-sided obstructive lesions.

Health care practitioners must approach women contemplating conception with a certain level of scrutiny because close to 15% of patients with heart disease in pregnancy have no history of a pre-existing condition.[1] Although the majority of women with known cardiac disease can have a successful pregnancy outcome, a multidisciplinary approach offers the best opportunity to decrease the risk of morbidity and mortality for both the mother and child.

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