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J. Am. Coll. Cardiol. 2011;58;337-350

doi:10.1016/j.jacc.2011.04.014

This information is current as of July 30, 2011

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<http://content.onlinejacc.org/cgi/content/full/58/4/337>

JACC

JOURNAL of the AMERICAN COLLEGE of CARDIOLOGY



STATE-OF-THE-ART PAPER

Pregnancy in Patients With Pre-Existing Cardiomyopathies

Kathleen Stergiopoulos, MD, PhD, Elaine Shiang, BA, Travis Bench, MD
Stony Brook, New York

To varying extents, women with pre-existing cardiomyopathies have a limited cardiovascular reserve. The hemodynamic challenges of pregnancy, labor, and delivery pose unique risks to this group of patients, which can result in clinical decompensation with overt heart failure, arrhythmias, and rarely, maternal death. A multidisciplinary team approach and a controlled delivery are crucial to adequate management of patients with underlying heart disease. Pre-conception planning and risk assessment are essential, and proper counseling should be offered to expectant mothers with regard to both the risks that pregnancy poses and the implications for future offspring. In this article, we will review the hemodynamic stressors that pregnancy places upon women with pre-existing cardiomyopathies and risk assessment and discuss what evidence exists with regard to the management of 2 forms of cardiomyopathy during pregnancy, labor, and delivery: dilated and hypertrophic cardiomyopathy. (J Am Coll Cardiol 2011;58:337-50) © 2011 by the American College of Cardiology Foundation

Hemodynamic changes that occur during pregnancy challenge the functional adaptability of the cardiovascular system in patients with pre-existing cardiomyopathies. The greater metabolic needs of pregnancy are met by changes in blood volume, peripheral vascular resistance, and myocardial function. In women with underlying cardiac disease, however, the demands of pregnancy pose additional stressors that can lead to decompensation, arrhythmias, and rarely, maternal death (1). Although heart disease is present in 0.5% to 1% of all pregnant women, data from the United Kingdom suggest that a cardiac etiology is the most common cause of death among pregnant women in the developed world (2,3). In a recent study that examined the outcomes of pregnant women with dilated cardiomyopathy, cardiac complications were common, accounting for approximately 39% of pregnancies (4). Heart failure was the most common complication, which typically occurred late in the pregnancy or post-partum. Additionally, pregnancy in women with pre-existing heart disease is associated with considerable morbidity and mortality (5), and although the incidence has been relatively constant over the past 2 decades, a slight increase has been noted recently. In this paper, we review the hemodynamic stressors that pregnancy places upon women with heart disease and risk assessment and discuss what evidence exists with regard to the management of dilated and hypertrophic cardiomyopathy

(HCM) during pregnancy, labor, and delivery. Pregnancy-related cardiomyopathy, or peripartum cardiomyopathy, will not be discussed, because this subject has been recently reviewed (6-10).

General Considerations

Hemodynamic changes during pregnancy. Dramatic changes occur to the cardiovascular system during pregnancy. Initially, marked increases in circulating blood volume are met with an increase in stroke volume and a 15% to 20% increase in heart rate. The net effect is a 30% to 50% increase in cardiac output by the end of the first trimester, an effect that peaks between the second and third trimesters (8,11). Another important consideration is the maturation of a placental circulation, which provides a substantial reduction in systemic vascular resistance. During the third trimester, preload reduction might occur due to compression of the inferior vena cava (IVC) by the gravid uterus, thus reducing cardiac output. Increases in cardiac output and intravascular volume allow 1 cardiac pump to feed both maternal and fetal tissues. It is indisputable that blood volume increases in pregnancy, but studies differ on when volume expansion levels off, if at all (1). Increases in blood volume enhance left ventricular end-diastolic volume, which peaks during the third trimester. This increased preload is thought to be due, in part, to an estrogenic effect, which creates higher circulating renin levels and greater sodium and water retention. Alternatively, hormones such as prolactin, human placental lactogen, prostaglandins, and growth hormone have also been implicated. During the early stages of pregnancy, increases in stroke volume are

From the Division of Cardiovascular Disease, Department of Internal Medicine, Stony Brook University Medical Center, Stony Brook, New York. The authors have reported that they have no relationships to disclose.

Manuscript received January 14, 2011; revised manuscript received March 24, 2011, accepted April 12, 2011.

**Abbreviations
and Acronyms****BNP** = B-type natriuretic peptide**COC** = combined hormonal contraceptive**HCM** = hypertrophic cardiomyopathy**IVC** = inferior vena cava**LVEF** = left ventricular ejection fraction**LVOT** = left ventricular outflow tract**NT-proBNP** = N-terminal pro-B-type natriuretic peptide**NYHA** = New York Heart Association**WHO** = World Health Organization

largely responsible for the observed increase in cardiac output, whereas later in pregnancy, an increased heart rate accounts for these changes. These physiologic effects are facilitated by the decreased systemic vascular resistance created by the placenta, a phenomenon that continues until the 32nd week of pregnancy when afterload begins to rise again. Besides the finding of elevated renin levels in the setting of an expanded intravascular volume, the integration of the renal and cardiovascular systems is also evident by the release of atrial natriuretic peptide and B-type natriuretic peptide (BNP) in response to atrial and ventricular distension, respectively (12).

Hemodynamic changes during labor and delivery. The cardiovascular system of women with heart disease is limited in its ability to accommodate the demands of pregnancy. These limitations become more evident during labor and delivery, where several changes in the circulatory system could result in hemodynamic decompensation (1). There is a catecholamine-induced increase in heart rate and stroke volume due to pain and anxiety. During the peripartum period, there can be an increase of cardiac output of up to 31% and approximately 50% in the second stage of labor. Abrupt changes in fluid balance result from a lack of IVC compression as well as the redistribution of blood from the lower limbs, particularly during uterine contractions. This rapid increase in preload can result in pulmonary congestion and clinical heart failure. Some of this intravascular volume is lost at delivery, where variable blood loss will occur—approximately 500 ml with a normal vaginal delivery, and 1,000 ml for a routine cesarean section. Further alterations in the hemodynamic status occur most commonly within the first 12 to 24 h post-partum. Within the first hour of delivery, cardiac output might continue to increase to as much as 80% above pre-labor values due to the relief of IVC compression and potentially rapid autotransfusion from the placenta (13). Moreover, further fluctuations in hemodynamic status can be due to the loss of the low resistance placenta and a relative increase in systemic vascular resistance as well as the mobilization of dependent edema and interstitial fluid. The use of anesthesia and analgesia can cause hypotension as a result of venous pooling and decreased systemic vascular resistance. Therefore, women with pre-existing cardiomyopathies might be at high risk for peripartum complications, due to the inability to accommodate increased cardiac output.

Pre-conception risk assessment and counseling. Women with cardiac disease require a complete pre-conception

evaluation and counseling to risk-stratify the maternal and fetal risks of pregnancy (Table 1). As such, appropriate evaluations can take place without putting the fetus at risk. A detailed history and physical examination, assessment of functional capacity and New York Heart Association (NYHA) functional class, and a 12-lead electrocardiogram are essential. Echocardiography is indicated in women with a history of valvular or congenital heart disease, significant dyspnea or any symptoms, any signs of heart failure, any systolic murmur grade >II, or any diastolic murmur. In addition, the etiology and degree of valvular regurgitation and/or stenosis, degree of pulmonary hypertension, and—if present—aortic root dilation can be quantified. Importantly, the left ventricular or systemic ventricular systolic function can also be determined. In certain congenital heart disease patients, assessment of the right heart size and function can be achieved most accurately with cardiac magnetic resonance imaging. Exercise stress testing can be useful to quantify the functional capacity of a patient if the history of the patient is unclear. However, this should ideally be performed before pregnancy. Poor functional status has been previously identified to be associated with maternal or fetal complications (14). Functional capacity might be an important predictor of the ability to tolerate a pregnancy, regardless of the underlying lesion. In a recent study examining pregnancy outcomes in women with congenital heart disease, an abnormal chronotropic response correlated with adverse pregnancy outcomes and could be considered in refining risk stratification schemes (15).

Women at particularly high risk include those with mechanical heart valves, Eisenmenger's syndrome, Marfan syndrome with aortopathy (aortic root >40 mm), and cardiomyopathy with reduced systemic ventricular function (left ventricular ejection fraction [LVEF] <40%) or a history of peripartum cardiomyopathy. In these women, pregnancy might be at prohibitive maternal risk and counseling with regard to avoidance of pregnancy might be ideal. Among pregnant women with known cardiac disease, poor prognostic factors include any of the following: prior cardiac events, prior arrhythmias, an NYHA functional class >II, peripheral cyanosis, significant valvular or outflow tract obstruction, and systemic ventricular dysfunction with LVEF <40% (16–18). Moreover, when 1 or more of these features are combined, the risk is more than additive (16–18). As such, a risk score has been developed by Siu et al. to identify predictors associated with the development of unfavorable cardiac events in pregnant women with heart disease and might be used to allow for the establishment of a plan of management for the antepartum, peripartum, and post-partum periods. If a woman has any 1 of the aforementioned poor prognostic factors, the estimated/expected risk is 27%, whereas if she has >1 risk factor, the risk rises to 75%. Women at elevated risk for adverse events should be managed by a multidisciplinary team at a tertiary care center equipped with the expertise to handle high-risk pregnancies (19). As part of a complete risk assessment, plans for monitoring, type of delivery, and anesthetic concerns should be addressed.

Table 1 Pre-Conception Evaluation and Risk Assessment

Thorough history of cardiac symptoms and physical examination
12-lead electrocardiogram
Baseline exercise tolerance and functional class (exercise testing if needed)
Baseline echocardiogram
Assessment of ventricular function (right and left)
Assessment of pulmonary artery pressure
Presence and degree of valvular dysfunction
Assessment of stability of cardiac hemodynamic status over time
Effective contraception until pregnancy desired
Adjust medications to prevent adverse fetal events
Genetics referral for patients with heritable cardiac lesion

Risk Stratification for Pregnant Patients With Cardiac Disease: High Risk for Adverse Maternal and Fetal Outcomes

Any prior cardiac event or arrhythmia
NYHA functional class >II
Systemic ventricular dysfunction (ejection fraction <40%)
Pulmonary hypertension (PA systolic pressure >50% systemic pressure), whether isolated or associated with severe valve disease
Left heart obstruction
Severe aortic stenosis (valve area <1 cm ² , Doppler jet velocity >4 m/s)
Symptomatic or severe mitral stenosis
Severe aortic or mitral regurgitation with NYHA functional class III or IV symptoms

NYHA = New York Heart Association; PA = pulmonary artery.

Pre-conception evaluation, risk assessment, and proper counseling are essential (20). Women with congenital heart disease, in particular, should be aware of adverse fetal and maternal outcomes as well as the genetic susceptibility of her offspring to heart disease. A study of women with congenital heart disease found that many of these women could not recall whether they were ever properly counseled by a health care provider or whether they were ever informed of an increased risk for maternal complications (21). Strict prenatal care and early risk stratification are fundamental measures to improve the prognosis of pregnancy in women with heart disease.

Contraceptive choices in women with heart disease. In women with heart disease, choice of contraception requires consideration of pregnancy risk, available contraception options as well as their risks and benefits, failure rates, understanding the consequences of unplanned pregnancy, and the preferences of the woman. Cardiologists are responsible, beyond risk assessment, for educating women about safe contraceptive options available as they relate to their cardiac condition. Interestingly, the current American College of Cardiology/American Heart Association guidelines for the management of adults with congenital heart disease suggests that it is the duty of the cardiologist to provide advice regarding informed decisions on contraception (22). Likewise, this recommendation could be extended to all women of childbearing age with heart disease. Moreover, understanding the risk of pregnancy is important to determine which type of contraception is required. Notably for example, for women with Eisenmenger’s syndrome, in which pregnancy is contraindicated due to prohibitively high maternal risks, permanent forms of sterilization can be considered.

Contraceptive options include: 1) combined hormonal contraceptives (COCs; estrogen/progestin formulations); 2) progestin-only formulations; 3), intrauterine devices; 4) barrier methods; and 5) sterilization/permanent forms of contraception. There are limited published reports addressing the issue of contraceptive use in women with heart disease (23,24). The most comprehensive guidance comes from a British working group that developed guidelines for the use of COCs in women with heart disease with the World Health Organization (WHO) format (23,25–27). Although both estrogen and progestins have adverse cardiac effects, the most clinically important are those of estrogens that cause thromboembolic events and hypertension. In this schema, there are 4 classifications for the use of COCs. The WHO Class 1 includes conditions where there is no restriction on the use of COCs, such as simple congenital lesions (successfully repaired atrial or ventricular shunts), and bicuspid aortic valve. The WHO Class 2 suggests that the benefits outweigh the risks of the use of COCs and includes conditions such as HCM without evidence of atrial arrhythmias and past cardiomyopathy that has fully recovered. Class 3 suggests that the risk of the use of COCs likely outweighs its benefits and includes bileaflet mechanical prosthesis in the mitral and aortic position while taking warfarin and atrial fibrillation or flutter while taking warfarin. Class 4 represents the highest-risk group for the use of combined estrogen and progestins and includes conditions such as cyanotic heart disease, prior left ventricular systolic dysfunction (LVEF <30%), and coronary artery disease or arteritis. A detailed description of methods of contraception and WHO Class 1 to 4 conditions can be found elsewhere (23).

In women with severe systemic ventricular dysfunction, maternal complication rates of pregnancy are high, and in many cases, pregnancy is contraindicated. However, due

to the potential for thromboembolic complications, combined hormonal contraceptives in the form of pills, transdermal patches, or vaginal rings are not recommended. In this group, progesterone-only forms of contraception and intrauterine devices are appropriate options. Although progestin-only forms of contraception are often suitable for women with severe cardiomyopathies, the oral form or the “mini-pill” has a high failure rate (5% to 10%) in the first year of use. Therefore, injectable or implantable versions of progestin-only formulations might be a better choice. In contrast, for women with HCM, the WHO classification of combined hormonal contraception is generally considered class 2, which is broadly usable.

Counseling women with heart disease with regard to contraception is being poorly done or not at all (21,28). In a survey of women with congenital heart disease, it was noted that only one-half of the women surveyed had recalled receiving specific information about contraception from a nurse or physician (21). In another recent study of women with congenital heart disease, many women do not use adequate methods of birth control (29). Consequently, there is room for improvement in this area.

Evaluation of heart failure in pregnancy. The normal physical examination in pregnancy can often mimic disease. Increased plasma volume might result in a systolic flow murmur, which can be heard in most normal pregnant patients. This murmur is usually systolic and soft (usually grade \leq II/VI). Moreover, distended or mildly increased neck veins, mild lower-extremity edema, and tachycardia are normal, commonly observed findings. In addition, common complaints of a normal pregnancy such as palpitations, fatigue, decreased exercise tolerance, and orthopnea can often be identical to those with occult or overt heart failure. During pregnancy, some patients might require careful, frequent follow-up evaluations, which might increase in frequency according to symptoms or severity of disease. Repeat echocardiographic imaging—perhaps as often as once/trimester or sooner as clinically indicated—can be helpful, because many symptoms of a normal pregnancy can mimic heart failure in the antepartum period. Due to an inability to increase cardiac output in the setting of an expanded intravascular blood volume, patients with an underlying cardiomyopathy often develop clinical heart failure, and therefore ongoing surveillance is valuable. Patients with left ventricular dysfunction might require restriction of activities, inpatient observation before delivery, and initiation or alteration of medical therapy.

Value of biomarkers in pregnancy. Limited data are available on the value of serum BNP or N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in pregnancy. In a small series of normal pregnant women, there were no significant differences in the mean BNP levels at various stages of pregnancy and the post-partum period (30–32). However, pregnant women had higher BNP levels that, although within the normal range, were approximately twice as high as nonpregnant levels. In women with pre-

eclampsia, levels of circulating atrial natriuretic and BNP are directly related to changes in left ventricular mass and volume (33). Now widely used to screen for ventricular dysfunction, BNP values in women with severe pre-eclampsia were found to be significantly higher than those from a normal study population, reflecting greater ventricular wall stress associated with this condition (31). Moreover, in a small series of pre-eclamptic women, diastolic left ventricular function was impaired, and levels of NT-proBNP were found to be increased, compared with that in normal pregnancies (34). In a more recent study, BNP values were higher in pregnant women with heart disease than without (35). In addition, among women with clinical events, all were found to have elevated BNP values, whereas no events occurred among women with a BNP value \leq 100 pg/ml. Thus, BNP had a negative predictive value of 100% for identifying events during pregnancy in this small series. However, a subset of women with elevated BNP values was identified without any clinical events, a finding of unclear significance. Certainly, most healthy pregnant women had low and stable concentrations of BNP throughout their pregnancy, suggesting that these women are able to compensate for the hemodynamic load of pregnancy. Although limited clinical data are available, measuring BNP or NT-proBNP levels seems to have clinical utility when the diagnosis of heart failure is in question (35).

Medical management of heart failure in pregnancy. The goals of medical therapy in chronic heart failure patients during pregnancy are similar to those of nonpregnant patients (36). Whenever possible, the continuation of chronic therapies that improve long-term outcomes in women with heart failure remains an important consideration. One important exception is that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are contraindicated in women who are pregnant or might become pregnant, due to the teratogenic effects on the fetal kidneys (Table 2) (8,37). Additionally, aldosterone antagonists should not be used in pregnant women. Providers should discontinue these medications ideally in women who are planning to become pregnant or as soon as pregnancy is confirmed. Women who are planning to become pregnant must weigh the risks of discontinuation of drugs that prolong survival in the setting of left ventricular dysfunction against the potential for teratogenicity, which is present throughout pregnancy, even during the first trimester (38). Women taking beta-blockers for the treatment of chronic heart failure should continue them during pregnancy, even if asymptomatic. Vasodilator therapy, when necessary, can be achieved with hydralazine or amlodipine, because there are published data supporting safety of these medications in pregnancy particularly in the setting of hypertension (39). Sodium restriction is recommended for all patients, whereas loop diuretics are indicated for the symptomatic relief of significant peripheral edema or pulmonary congestion. Moreover, digoxin can be added or continued during pregnancy for the symptomatic relief of

Table 2 Medical Management of Chronic Heart Failure in Pregnancy

Drug/Class	Purpose	Comment
Diuretics		
Furosemide	Generally reserved for treatment of pulmonary edema Use of lowest possible dose	Can result in uteroplacental hypoperfusion Contra-indicated in settings in which uteroplacental hypoperfusion is already reduced (IUGR, pre-eclampsia) FDA class C*
Digoxin	Not considered first-line therapy for heart failure in nonpregnant patients No improvement in mortality Considered useful in pregnancy, given limitations of medical armamentarium	Generally considered safe Useful in treatment of persistent symptoms, despite standard therapy FDA class C
Vasodilators		
Hydralazine	Commonly used oral antihypertensive agent in pregnancy Can be substituted for ACE inhibitor during pregnancy	Demonstrated efficacy in hypertension Risk of hypotension Pregnancy already reduces SVR Avoid large or precipitous decreases in blood pressure FDA class C
ACE inhibitors/ARB	Proven benefit in treatment of chronic heart failure in nonpregnant patients	Contraindicated throughout pregnancy due to teratogenic effects. Associated with oligohydramnios, neonatal death secondary to renal failure, renal agenesis. FDA class C for first trimester; class D for second and third trimesters
Amlodipine	Alternative to ACE inhibitor in pregnancy	Can be used with hydralazine if needed FDA class C
Nitrates	Might be used to treat decompensated heart failure	FDA class C
Beta-blockers		
Carvedilol, labetalol, metoprolol, atenolol	Essential component to chronic heart failure therapy Agents that are beta-1 selective are preferable Beta-blockers should be continued throughout pregnancy	Generally safe and effective in pregnancy Can cause IUGR Infants born to mothers taking beta-blockers should be observed for at least 72 h after birth FDA class C
Aldosterone antagonists		
Spirolactone, epleronone	Prolong survival in selected heart failure patients Not routinely used in pregnancy	No data to support safety in pregnancy FDA class D
Warfarin	Risk/benefit ratio needs to be discussed with the patient for treatment and prophylactic anticoagulation in severe left ventricular dysfunction	First trimester teratogenesis Dosing is complicated in pregnancy FDA class X

*U.S. Food and Drug Administration (FDA) class: A (controlled studies show no risk), B (no evidence of human risk in controlled studies), C (risk cannot be ruled out), D (positive evidence of risk), X (contraindicated in pregnancy).

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; IUGR = intrauterine growth retardation; SVR = systemic vascular resistance.

heart failure symptoms, after beta-blockers and vasodilators have been maximized.

In the setting of acute decompensation of heart failure, particularly if severe, therapies are directed similarly to nonpregnant women. Intravenous diuretics and intravenous vasodilator therapy with nitroglycerin can be used safely. Right heart catheterization might be necessary, if the diagnosis of heart failure is in question on the basis of physical examination or when large shifts in hemodynamic status are anticipated (as in labor and delivery). Right heart catheterization is uncommonly used in the setting of pregnancy.

Dilated Cardiomyopathy

Dilated cardiomyopathy is defined as reduced left ventricular systolic function in the absence of coronary, valvular, congenital, or systemic disease known to cause myocardial dysfunction

(40). Affected patients might even have impaired systolic function in the absence of any symptoms. Currently, dilated cardiomyopathy is responsible for approximately 10,000 deaths and 46,000 hospital stays each year in the United States and is the most common indication for cardiac transplantation (41). Although there are several known causes of dilated cardiomyopathy (Table 3), the etiology remains undefined in approximately 50% of cases (42) (Figs. 1 and 2).

Women with dilated cardiomyopathy have traditionally been advised to avoid pregnancy. This dictum is largely based on data derived from studies in patients with peripartum cardiomyopathy and the observation of poor peripartum maternal and fetal outcomes in this group (16–18). Dilated cardiomyopathy has been associated with A-type lamin gene defects, which are associated with a high rate of heart failure and life-threatening arrhythmias, as predicted by NYHA functional class and

Table 3 Etiology of Dilated Cardiomyopathies

Idiopathic: 50%
Myocarditis: 9%
Viral cardiomyopathy
Chagas disease
Lyme disease
HIV infection
Ischemic heart disease: 7%
Infiltrative disease: 5%
Sarcoidosis
Peripartum cardiomyopathy: 4%
Hypertension: 4%
HIV infection: 4%
Connective tissue disease: 3%
Systemic lupus erythematosus
Substance abuse: 3%
Alcohol-related
Cocaine
Chemotherapy: 1%
Adriamycin
Doxorubicin
Trastuzumab
Other: 10%
Stress-induced (Tako-tsubo) cardiomyopathy
Noncompaction
Hypertrophic cardiomyopathy
Tachycardia-mediated cardiomyopathy
Endocrine related (thyroid dysfunction, acromegaly, pheochromocytoma)
Inherited/familial cardiomyopathy
Obstructive sleep apnea

Adapted from Felker et al. (42).
HIV = human immunodeficiency virus.

the type of mutation (43). The increase in intravascular volume and cardiac output during pregnancy leads to a greater risk for complications in women with dilated cardiomyopathy, particularly in the third trimester during a period of maximal hemodynamic burden. A history of cardiac events including previous episodes of heart failure, atrial fibrillation or flutter, transient ischemic attack, or a history of cardiac events before pregnancy was highly predictive of pregnancy-related cardiac outcomes (16). Heart failure, arrhythmias, and stroke were more common in women whose LVEF was <40% (18).

There is insufficient evidence relating to specific etiologic factors to determine whether pregnancy might be better-tolerated in certain cardiomyopathies compared with others. In a small retrospective cohort study comparing patients with peripartum cardiomyopathy with patients with dilated cardiomyopathy, those with peripartum cardiomyopathy had uniformly worse outcomes (44). These included 3 maternal deaths and 4 heart transplantations in the peripartum group, compared with 1 transplantation in the dilated cardiomyopathy group. None of the dilated cardiomyopathy patients had a significant decline in cardiac status. In contrast, a study of 26 women from Brazil suggested that cardiac complications were higher in the idiopathic cardio-

myopathy cohort when compared with those with persistent left ventricular dysfunction due to peripartum cardiomyopathy (45). A study from Haiti identified 99 women with peripartum cardiomyopathy, 15 of whom had subsequent pregnancies. One-half of these women experienced worsening heart failure and long-term systolic dysfunction (46). However, all 3 studies suffer from retrospective design issues and selection bias.

Maternal cardiac, obstetric, and fetal outcomes in women with dilated cardiomyopathy were examined in a recent study by Grewal et al. (4). Thirty-six pregnancies in 32 women were evaluated as part of a larger prospective study on outcomes in women with heart disease. Age-matched outcomes were compared with nonpregnant women with underlying cardiomyopathies. Notably, 39% of the pregnancies were complicated by at least 1 maternal cardiac event. In the multivariate analysis, moderate or severe LV dysfunction and/or NYHA functional class III or IV were the main determinants of adverse maternal cardiac outcomes. In particular, the subset of women with moderate or severe left ventricular dysfunction had the worst 16-month event-free survival. In women without moderate or severe LV systolic dysfunction, NYHA functional class III or IV, and/or previous cardiac event, no adverse events were observed. However, if any 1 of these 3 factors was present, the risk of an adverse event was 64%. Moreover, the investigators found that the event rate for adverse neonatal events was highest among women with both obstetric and cardiac risk factors combined (43%).

Patients with known left ventricular dysfunction (LVEF <40%) are at high risk for adverse maternal and fetal events and should be advised against pregnancy. Of particular concern, women with prior peripartum cardiomyopathy in whom left ventricular function has returned to normal (LVEF >50%) still remain at significant risk for morbidity and mortality with a subsequent pregnancy (47). In addition, patients with class III or IV symptoms and moderate-to-severe left ventricular dysfunction in the first or second trimester can be considered for termination of pregnancy.

Management of labor and delivery in dilated cardiomyopathy patients. A multidisciplinary team is crucial to adequate management of patients at the time of labor and delivery. Consultation among the obstetrician, obstetrical anesthesiologist, and the cardiologist is recommended before initiation of labor and delivery. In addition, patients with heart failure or underlying cardiomyopathy should be monitored carefully throughout labor and delivery as well as in the early post-partum period, when hemodynamic decompensation is most likely to occur. This includes continuous maternal electrocardiographic monitoring and noninvasive blood pressure monitoring. Invasive central monitoring such as right heart catheterization and arterial line monitoring can be employed on an individual basis. Arterial line monitoring is considered helpful and low-risk. Right heart catheterization, although not required, might be needed to optimize hemodynamic status when large shifts in

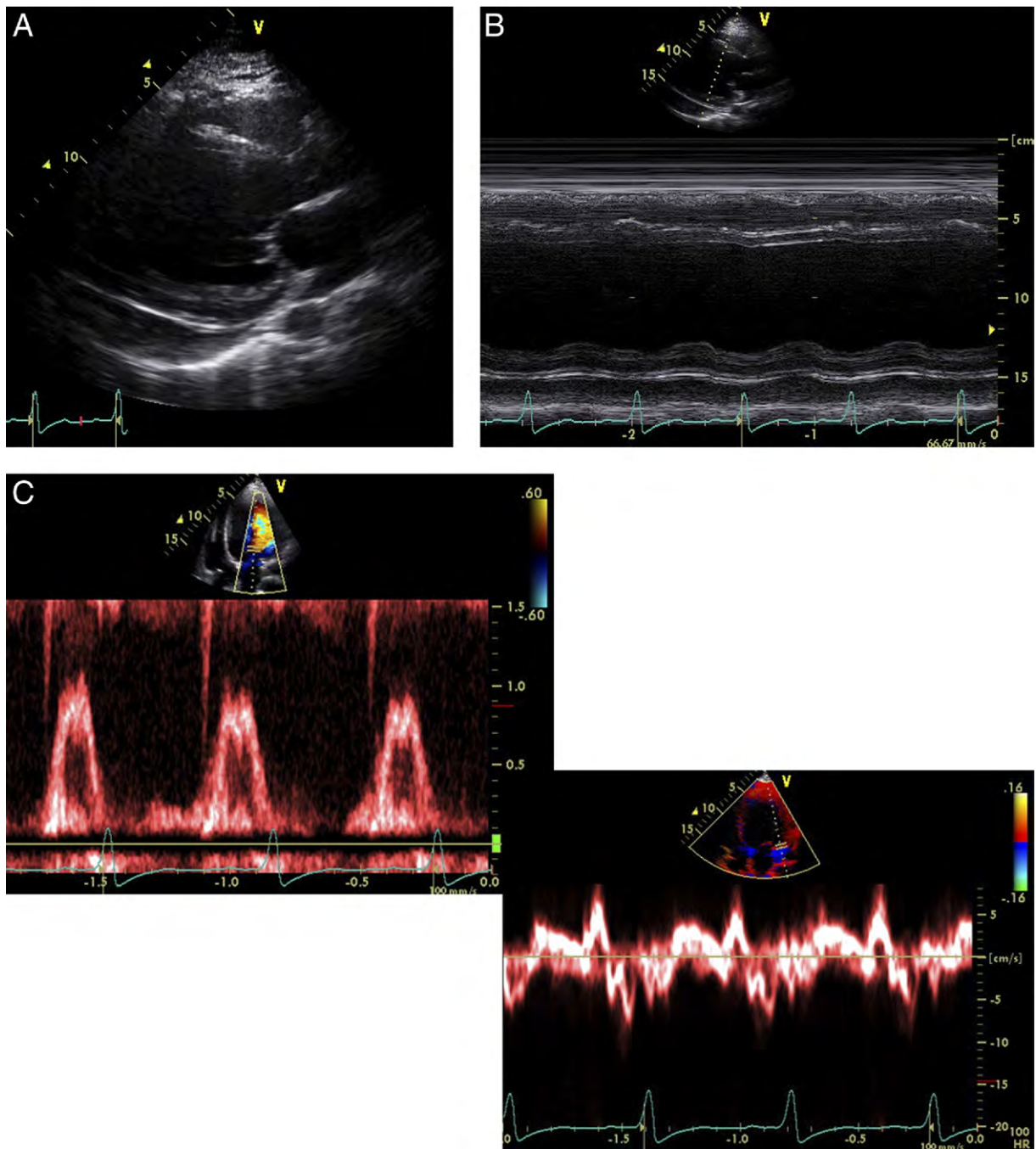


Figure 1 Example of Decline in Left Ventricular Systolic Function

A 28-year-old woman, with a history of viral cardiomyopathy with severely reduced left ventricular ejection fraction, presented at 21 weeks of gestation. Her medical history was complicated by asthma, obesity, presumed obstructive sleep apnea, diabetes, and active tobacco and drug abuse, and an implantable cardioverter-defibrillator had been placed for primary prevention of sudden cardiac death. She was considered, upon risk assessment, at prohibitively high risk for adverse maternal and fetal outcomes but adamantly refused termination of pregnancy despite extensive counseling. She was hospitalized for congestive heart failure at 26 weeks, which was managed with in-hospital bed rest and medically with digoxin, carvedilol, hydralazine, and furosemide. She developed worsening heart failure and worsening left ventricular systolic function (left ventricular ejection fraction declined from 25% to <10%) at 28 weeks of gestation and was delivered by urgent cesarean section with an epidural and sedation and placement of a pulmonary artery catheter and arterial line. Of note, the wedge pressure of the patient was 28 mm Hg at the beginning of the procedure. Her post-partum course was complicated by a transient ischemic attack. (A) Parasternal long-axis view demonstrating severe left ventricular dilation and tethering of the mitral leaflets. (B) M-mode of the left ventricle demonstrating severe left ventricular systolic dysfunction. In addition, she has a small-to-moderate posterior pericardial effusion without hemodynamic significance, a common finding in pregnancy. (C) Diastolic parameters of mitral inflow E and A waves and severely reduced lateral tissue Doppler velocities, consistent with restrictive physiology and elevated filling pressures, which progressed from pseudonormal diastolic function early in pregnancy.

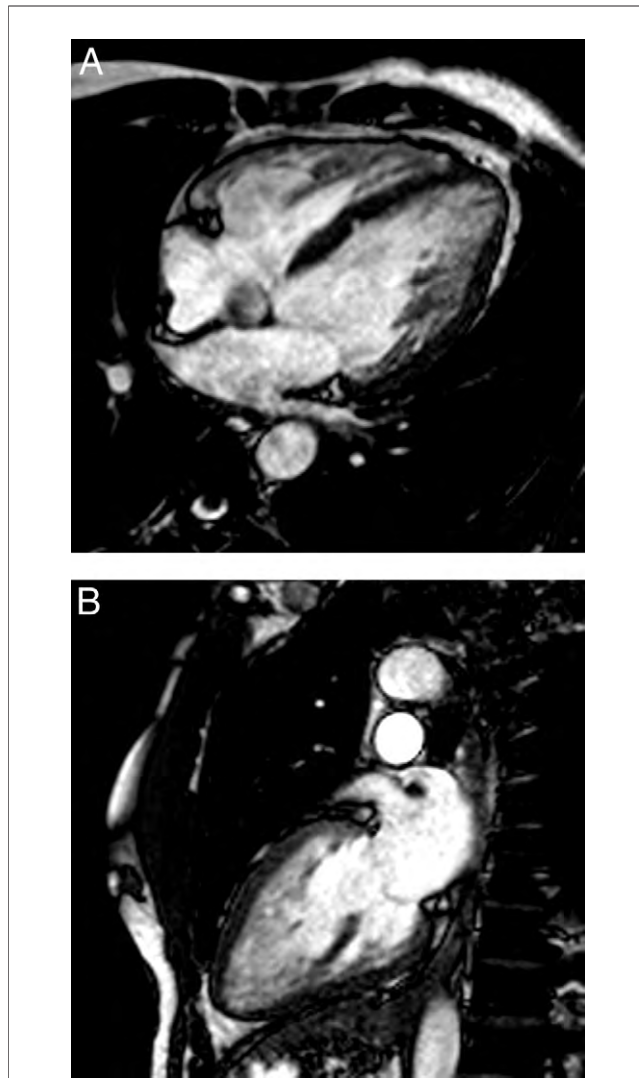


Figure 2 Cardiac Magnetic Resonance Imaging Demonstrating Morphological Noncompaction

Criteria include a maximal end-systolic ratio of noncompacted endocardial thickness to compacted epicardial layer thickness (N/C) ≥ 2 (here, seen most prominently in the lateral wall of the left ventricle). Isolated noncompaction of the left ventricle can also present in the peripartum period as the first episode of heart failure, arrhythmia, or embolic event. Underlying noncompaction might be present in asymptomatic antepartum patients, who cannot tolerate the hemodynamic stress of pregnancy, resulting in clinical decompensation. Such a presentation might be confused with peripartum cardiomyopathy, which can have a similar clinical course. (A) 4-chamber view. (B) 2-chamber view. Both views demonstrate noncompacted myocardium.

volume are anticipated, such as during a cesarean section or when there is evidence of clinical instability (19). Although no official recommendations exist, right heart catheterization is occasionally used in pregnant women with severe clinical heart failure and/or severely reduced left ventricular systolic function at the time of delivery.

The decision regarding the timing and mode of delivery is made on the basis of the hemodynamic status of the patient (Table 4). Early delivery is not required in all patients with cardiomyopathies or heart failure. The deci-

sion is made on the basis of the failure of the patient to respond to medical therapy and the overall hemodynamic status of the patient. The issue of the timing of delivery for critically ill pregnant women with heart failure requires a coordinated decision between the cardiologist, obstetrician, and anesthesiologist that balances the risks of continuing a pregnancy to the mother and fetus versus the risk of delivery and how that delivery should take place. If the heart failure of the patient is refractory to medical therapy, delivery needs to be strongly considered. Because no official recommendations exist, an individualized approach is sought. Virtually all pregnant women with cardiac disease should expect an attempt at vaginal delivery, unless obstetric contraindications exist. For women with pre-existing cardiac disease, a vaginal delivery poses less cardiac risk, because cesarean delivery is accompanied by approximately twice as much blood loss. Patients who are considered stable from a cardiac perspective can be allowed to spontaneously progress

Table 4 Management During Labor and Delivery

Decision regarding timing and mode of delivery
Management during labor and delivery and post-partum concerns
Short vaginal delivery with excellent anesthesia, with consideration of assisted second stage of labor
Left lateral decubitus position
Cesarean section per obstetric indications
Invasive monitoring if needed (right heart catheterization, invasive arterial blood pressure monitoring)
Medical therapy optimization of loading conditions
Monitoring and treatment of pulmonary edema
Anesthetic choices for labor and delivery in the setting of heart failure
General anesthesia
Volatile agents include sevoflurane, isoflurane, and desflurane, which can decrease SVR
Reserved for emergency situations
Rapid sequence induction can lead to cardiovascular instability
Mortality is highest at the time of induction and intubation
Regional anesthesia
Includes spinal, epidural, or combined spinal-epidural
Technique of choice in patients with heart failure and pregnancy for delivery
Offers afterload reduction and blunts hemodynamic response of labor and delivery
Low concentration of bupivacaine and lipophilic opiates allow for hemodynamic stability
Sedation
Can accompany regional techniques if needed
Agents such as propofol, midazolam, and fentanyl have been used without fetal issues
Aspiration risk exists
Post-partum concerns
Consider treatment of severe anemia
Medical therapy to optimize loading conditions (treatment of pulmonary edema)
Hemodynamic and telemetry monitoring for 12-24 h
Contraception or sterilization consideration
Future consideration of ICD*

*Indications for insertion of an implantable cardioverter-defibrillator (ICD) would follow accepted guidelines (48).

SVR = systemic vascular resistance.

through the various stages of labor. However, if there are concerns about the functional adequacy of the heart and circulation, labor can be induced under controlled conditions. The timing of induction can be individualized, taking into account the cardiac status of the patient, inducibility of the cervix, and fetal lung maturity. From a practical point of view, it is useful to plan the induction so that delivery occurs during a time when all services are available. In general, a long induction in a woman with an unfavorable cervix should be avoided. Induction of labor in a patient with a favorable cervix usually requires only oxytocin administration and artificial rupture of membranes. An unfavorable cervix, however, should be treated with a prostaglandin E analogue. Even this should be done cautiously in women with underlying cardiomyopathies, because prostaglandin analogues might be absorbed systemically, causing unwanted hemodynamic consequences, including a decreased systemic vascular resistance and reflex tachycardia (49). In a recent study of patients with dilated cardiomyopathy, most deliveries were vaginal (81%), and the most frequently used form of anesthesia was epidural anesthesia (86%) (4). Indications for cesarean delivery were unrelated to pre-existing cardiac disease in any 1 of these patients. As would be expected, fetal/neonatal event rates were higher in women with at least 1 obstetric risk factor, including a history of premature delivery or rupture of membranes, an incompetent cervix, or the need for cesarean delivery. Smoking, anticoagulation use, multiple gestation, and maternal age <20 or >35 years were nonobstetric risk factors that were also associated with increased fetal/neonatal events.

Anesthetic considerations in pregnant women with chronic or new onset heart failure require a specialized approach and, when possible, should be planned in the antepartum period. Women with cardiomyopathy and/or evidence of clinical heart failure should not expect a trial of natural childbirth without the use of some form of anesthesia when a vaginal delivery is decided upon. The goal of the anesthetic agents is to blunt the physiologic increased metabolic demands and hemodynamic stress that normally accompanies labor and delivery. The goals of management are mainly to avoid excessive anesthetic-induced myocardial depression, maintain normovolemia, and minimize the inherent sympathetic stimulation associated with labor (19). A combination of intravenous opiates and lumbar epidural anesthesia are highly effective to relieve pain during labor and delivery and is considered the technique of choice. Epidural anesthesia, if introduced slowly and carefully, produces changes in pre-load and afterload that can be advantageous in the setting of reduced ventricular function. It provides excellent operative analgesia, thus limiting pain-induced elevations of sympathetic activity, but also reduces the maternal urge to push (Valsalva maneuver). Additionally, the accompanying venodilation reduces venous return, which might also be favorable for those patients with evidence of volume overload. Decreases in systolic blood

pressure might require treatment with vasoactive agents rather than intravenous fluids. Alternatively, the use of general anesthesia incurs the risks of hemodynamic instability associated with systemic anesthetic administration as well as adequate sedatives to tolerate endotracheal intubation.

Once in labor, women with cardiac disease should be placed in a left lateral decubitus position to avoid IVC compression by the gravid uterus. The obstetrician should allow the fetal head to descend to the perineum without maternal assistance, an attempt to avoid the undesirable circulatory effects of the Valsalva maneuver. The second stage of labor can be shortened via assistance with low forceps or by vacuum extraction as needed. Throughout this process, the clinical scenario should dictate the need to abandon further attempts at vaginal delivery and to proceed with cesarean delivery.

Post-partum considerations. After delivery, uterine bleeding is controlled naturally by continued uterine contractions from posterior pituitary oxytocin secretion. Synthetic oxytocin is often administered to augment these effects but should be infused slowly to avoid hypotensive effects. Hemodynamic monitoring of the mother should continue for at least 12 to 24 h after delivery, because volume redistribution during this time period causes rapid intravascular volume shifts. If severe anemia is present, often related to dilutional anemia of pregnancy, exacerbated by blood loss at delivery, treatment could be considered with iron supplementation or blood transfusion in an effort to relieve tachycardia and decrease myocardial work. Other post-partum considerations are listed on Table 4.

Although inciting events are difficult to define, pregnancy seems to affect the natural history of dilated cardiomyopathy, particularly over the short term (4). Cardiac complications such as worsening heart failure accompanied by worsening LVEF, arrhythmias, and cerebrovascular accidents were noted to occur most commonly in pregnant women studied late during their pregnancy as well as in the first 16 months post-partum. It is known that the third trimester and early post-partum periods are times of maximum hemodynamic change, supporting the concept that accelerated changes in hemodynamic load can precipitate cardiac decompensation. But even beyond hemodynamic fluctuations, a transient decline in left ventricular contractility during pregnancy has even been described, which might be even more important in patients with poor cardiac reserve (50). It also seems that this decline in left ventricular systolic function might not be reversible (an example of which is shown in Fig. 1). An important issue seems to be the continuation of optimal medical therapy for heart failure during pregnancy, which is not possible secondary to the teratogenic effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. The hemodynamic load of pregnancy and delivery, coupled with the prolonged discontinuation of optimal medical therapy during pregnancy, often because of contraindications or patient prefer-

ence, might also predispose to further late negative effects on ventricular function (4,51).

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is an autosomal dominant disease due to mutations of the cardiac sarcomere proteins. This type of cardiomyopathy has a phenotypically variable course and is diagnosed with a frequency of approximately 1 in 500 of the adult population (52,53). Morphological and functional features include asymmetric hypertrophy of the left ventricle, a nondilated left ventricular cavity, and preserved systolic function with impaired diastolic function (Fig. 3) (54–57), whereas myofibrillary disarray is the hallmark pathologic feature. Although no evidence of obstruction is present in the majority of patients with HCM, a left ventricular outflow tract (LVOT) obstruction is present at rest in approximately 20% of patients (58). Left ventricular outflow tract obstruction is directly related to the severity of hypertrophy of the basal septum, which obstructs the contours of the LVOT. Secondary causes of dynamic outflow obstruction occur as the result of a venturi effect in the narrowed outflow tract, causing systolic anterior motion of the mitral valve (52). Diastolic dysfunction is frequently present due to impaired relaxation of the left ventricle. Both atrial and ventricular arrhythmias can coexist with HCM, leading to palpitations and sudden cardiac death as well as embolic stroke, worsening diastolic heart failure, and dyspnea. With the increased use of echocardiography and genetic and family screening, more women of child-bearing age are being diagnosed with HCM.

Screening. The clinical diagnosis of HCM is usually accomplished with an integration of history, physical examination, electrocardiography, and echocardiography. There is phenotypic heterogeneity of patients with HCM, because the distribution of left ventricular hypertrophy is inconsistent, with no single morphologic expression considered to be “typical.” Anteroseptal hypertrophy is most frequently involved, whereas patterns such as concentric hypertrophy or pure apical involvement are less common (59). Echocardiography typically demonstrates a hypertrophied, nondilated left ventricle with an observed wall thickness of ≥ 15 mm, in the absence of any other cardiac or systemic disease known to cause increased wall thickness. Left ventricular outflow tract obstruction is assessed by the measured gradient as estimated by Doppler flow analysis and the degree of systolic anterior motion of the mitral valve. A Doppler-derived pressure gradient of 30 mm Hg or more usually correlates with symptoms (53). Mitral regurgitation is commonly observed by echocardiography and is due to mitral valve abnormalities related to systolic anterior motion of the mitral valve (Fig. 3).

Although screening for the usual echocardiographic criteria for HCM is commonplace, the landscape is changing with regard to clinical evaluation and screening for this

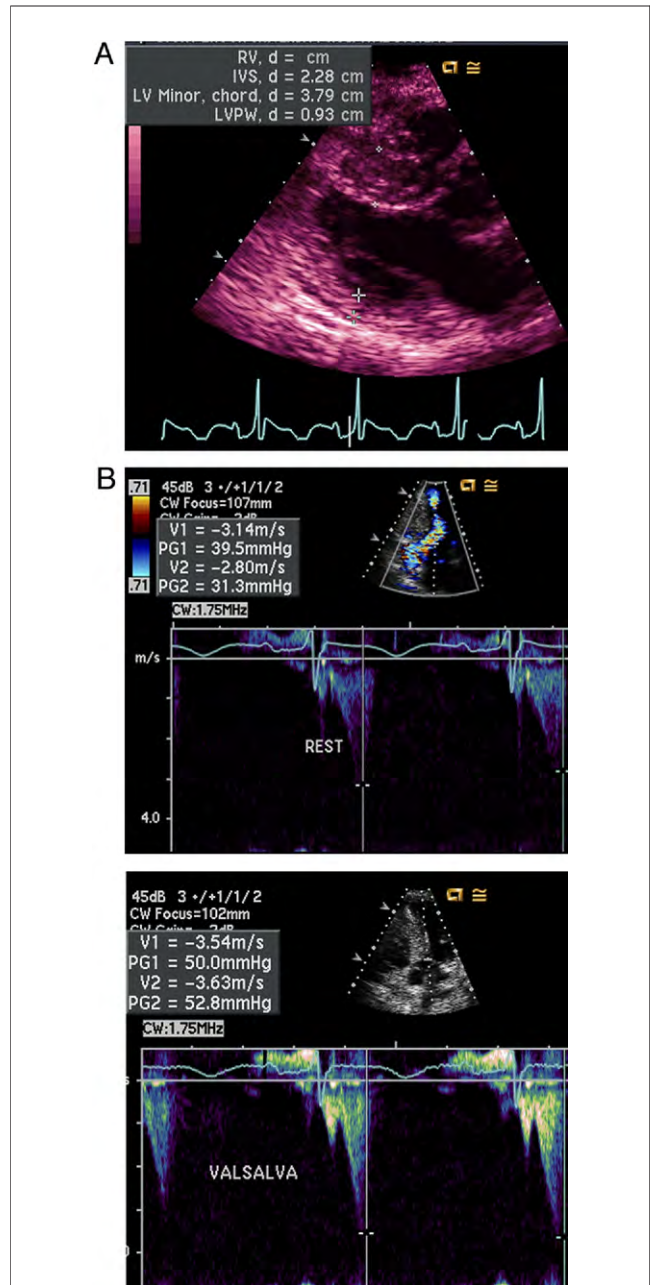


Figure 3 2-Dimensional Transthoracic Echocardiography in HCM

(A) Parasternal long-axis view of a hypertrophied, nondilated left ventricle (LV). Septal wall thickness is ≥ 15 mm. (B) Doppler flow analysis of LV outflow tract. A resting gradient of 39 mm Hg increases to 50 mm Hg with Valsalva maneuver. The increased blood volume as pregnancy progresses can allow for a normalization of the nondilated LV in hypertrophic cardiomyopathy (HCM), which often lessens the degree of obstruction in the left ventricular cavity. However, if mitral regurgitation is present, the increase in blood volume can worsen the degree of regurgitation as pregnancy progresses. Mitral regurgitation, even if severe, is often well-tolerated in pregnancy due to the reduced systemic vascular resistance already present in pregnancy and low resistance circuit of the placenta. IVS = interventricular septum; LVPW = left ventricular posterior wall; RV = right ventricle.

disease process and might involve routine genetic screening in the near future. To date, molecular genetics have identified at least 11 individual genes found to be responsible for

a hypertrophic phenotype, representing several hundred individual mutations within genes coding for various sarcomeric proteins, the most common of which are beta-myosin heavy chain and myosin binding protein C (60,61). With the identification of causal genes came the understanding that one-half of these cases are familial, whereas the others are felt to be due to sporadic mutations. Familial cases exhibit classic Mendelian genetics and are transmitted in an autosomal dominant fashion. Despite our increased understanding of this disease, a definitive genetic causality can be found in only 40% of cases. Moreover, there are likely many more responsible mutations yet to be identified, and our understanding of the phenotypical expression of these gene defects is also changing (62). Notably, among patients with seemingly identical genotypes, the expression of these mutations is remarkably variable. Some genetically prone individuals might not manifest phenotypically identifiable disease until later in adult life (63). Such implications are important in the family planning of any patient with HCM, where there is a 50% chance of producing an affected child. Counseling should include the need for genetic screening of known mutations and, potentially, for lifelong clinical and echocardiographic follow-up.

Risks in pregnancy. The risks of HCM and pregnancy are due to hemodynamic deterioration, arrhythmias, or sudden cardiac death. Most women with HCM who experience no or mild symptoms before pregnancy will likely tolerate pregnancy well (52,53,64). The increased blood volume and stroke volume of pregnancy usually result in a mild dilation of the left ventricular end diastolic dimension and, thus, lowering of the dynamic outflow tract gradient. However, a small subset of patients, with moderate or severe symptoms before pregnancy, are at increased risk for cardiac events. The higher the LVOT gradient is before pregnancy or during the first trimester, the higher the likelihood that symptoms will progress. Moreover, the subset of patients with severe LVOT obstruction (those with a gradient of >100 mm Hg) are at the highest risk of hemodynamic deterioration during pregnancy (52).

Sudden death is a recognized complication of HCM during pregnancy, particularly in patients with severe outflow tract obstruction or in those with other significant risk factors for sudden cardiac death (53). Major risk factors include previous out-of-hospital arrest or documented sustained ventricular tachycardia, or a strong family history of HCM with associated sudden death. Minor risk factors for sudden death include severe septal hypertrophy (>3 cm), nonsustained ventricular tachycardia on Holter monitoring, and a decrease in blood pressure with exercise.

Management in pregnancy. Although most patients with HCM are asymptomatic, common symptoms that women with HCM experience during pregnancy include exertional chest pain, fatigue, dyspnea, palpitations, and syncope. When these symptoms are reported during pregnancy, however, most women note experiencing similar symptoms before pregnancy as well (64). Sudden death might also be

the initial presentation of undiagnosed disease. Dyspnea on exertion is the most common symptom, mainly owing to diastolic dysfunction and outflow tract obstruction. As a result, there is a potential for clinical heart failure among pregnant women (53). However, for the majority of patients, the hemodynamic changes that occur are usually well-tolerated in pregnancy. Although the overall decrease in systemic vascular resistance during pregnancy might be detrimental in HCM patients, this is usually offset by the increase in intravascular volume. Although HCM patients are sensitive to alterations of intravascular volume and cardiac rate and rhythm, the increase in intravascular volume and stroke volume actually reduces LVOT obstruction. Diastolic dysfunction is common in HCM patients who are more likely to develop pulmonary edema, aggravated by mitral regurgitation, which occurs secondary to systolic anterior motion of the mitral valve (65).

If symptoms of heart failure develop during pregnancy, it is indicative of poor functional class before pregnancy, because clinical deterioration is twice as likely to occur in patients with antenatal outflow obstruction as in those without. The higher incidence of heart failure in some patients has been attributed to the genetic heterogeneity of the disease (66). Most women who progress to NYHA functional class III or IV heart failure were previously symptomatic, just as patients who experienced atrial fibrillation or syncope experienced similar symptoms before pregnancy. Thus, despite a reduced left ventricular cavity size and poor left ventricular compliance, women with HCM seem to be able to tolerate the hemodynamic burdens associated with pregnancy. Studies have suggested a similar incidence of cardiac events between nonpregnant and pregnant patients, suggesting that pregnancy does not alter the clinical course of women with HCM.

There are few available data describing the optimal management of pregnant women with HCM. Table 5 offers some general considerations for management. Studies by Thaman et al. (64) and Autore et al. (53) show that approximately one-quarter to one-third of pregnant patients were receiving medications for symptomatic HCM—beta-blockers being the most common. Although beta-blocker and calcium-channel blocker use has been described as safe in this population, with little effect on fetal outcome, some of the women discontinued these medications during pregnancy due to the potential for adverse fetal events. In women who received medications before pregnancy, discontinuing medications before or early in pregnancy was not shown to precipitate significant clinical deterioration (64).

In a study by Autore et al. (53), the maternal mortality for patients with HCM was increased compared with that of the general population. The absolute maternal mortality was low, however, and seemed to be principally confined to women at particularly high risk. Two maternal mortalities were described in 100 women over the course of 199 live births. Both women died suddenly, and both were known to be symptomatic before pregnancy. In the presence of a

Table 5 General Considerations for Management of Pregnant Women With Hypertrophic Cardiomyopathy

Assessment of symptoms and functional status before pregnancy
Determine the degree of LVOT obstruction at rest and with Valsalva maneuver (by echocardiogram) to identify those with severe obstruction
Risk stratification of sudden cardiac death
Institute medical therapy for symptomatic patients with beta-blockade (verapamil as an alternative)*
Avoidance of decrease in preload (straining, dehydration, diuretics only if needed)
Left lateral decubitus position
Avoid inotropes and vasodilators
For the hypotensive patient, balance fluids and vasopressor agents

*Verapamil is not considered safe in patients with severe resting left ventricular outflow tract (LVOT) obstruction.

favorable risk profile as assessed clinically, Autore et al. (53) found that the progression of symptoms, the development of atrial fibrillation, and syncope were uncommon during pregnancy. In another study by Thaman et al. (64) of 127 women and 271 pregnancies, the overall complication rate was low, and pregnancy was tolerated well. Approximately 28% of women reported cardiac symptoms during pregnancy, with most of them reporting similar symptoms before pregnancy. In this group, there was no symptomatic deterioration. Two patients developed clinical heart failure during the post-partum period, but there were no maternal deaths. Unfortunately, there were 3 unexplained intrauterine deaths, all occurring in women taking cardiac medications. Moreover, in a retrospective study of 41 women over the course of 132 pregnancies, there were no maternal deaths and no aggravation of symptoms (67). Therefore, there seems to be a subset of patients who are at higher risk of sudden death or heart failure, who would potentially benefit from aggressive risk stratification. Thus, although most women with HCM can safely tolerate pregnancy, it is important to have an appreciation of the underlying pathology and to identify those at particularly high risk when managing these patients.

Management during labor and delivery. Although pregnancy seems to be well-tolerated in HCM, the physiologic changes that occur during labor and delivery seem to be more problematic. During labor, a catecholamine-induced increase in heart rate and stroke volume increase cardiac output. As noted previously, tachycardia shortens the left ventricular diastolic filling period, decreasing preload, and exacerbates outflow obstruction. Moreover, performance of the Valsalva maneuver during labor and delivery, which helps the fetus descend during the second stage of labor, can also impair venous return and impairs cardiac output in patients with significant obstruction (68). A similar problem can occur in the setting of substantial blood loss during or after delivery (69).

It is generally accepted that patients with HCM should deliver at a high-risk center, with expertise in the management of this condition. Beta-blockers are particularly useful during labor and delivery, because these agents blunt the

normal increases in heart rate and contractility, allowing for adequate diastolic filling, which might decrease the outflow tract obstruction (66). Low-dose diuretics might be necessary if pulmonary edema develops, but aggressive diuresis can result in a reduction of intravascular volume and blood pressure, leading to a reduction in preload and potential worsening LVOT obstruction (52). Because of the sensitivity of HCM patients to disturbances in intravascular volume and blood pressure, epidural anesthesia should be avoided due to the potential for hypotension, but vaginal deliveries with regional anesthesia have been documented. Likewise, the use of prostaglandins for the induction of labor is not advised, secondary to inherent vasodilatory effects. Normal vaginal delivery is considered safe, whereas cesarean section is reserved for emergency situations (69). In the U.K. registry of high-risk obstetric anesthesia between the years of 1997 and 2001, there were 26 patients with an underlying cardiomyopathy. Of those with HCM, 75% of these patients were delivered by caesarian section and received general anesthesia (70). Most women received general anesthesia out of concern for a rapid fall in systemic vascular resistance in patients with a fixed cardiac output due to the degree of outflow stenosis. Vasopressor agents and fluids can be given to treat hypotension, but it is preferable to use a pure alpha-agonist such as phenylephrine, because it lacks any inotropic properties (68). In HCM, inotropes can worsen the outflow gradient and are relatively contraindicated (51).

Conclusions

In women with underlying cardiomyopathy, changes in intravascular volume, cardiac output, and peripheral vascular resistance coupled with an impaired ventricular reserve pose unique challenges in the management of pregnancy, labor, and delivery. Pre-conception risk assessment and proper counseling with regard to the safety of pregnancy is crucial, but more data are necessary to provide more informed recommendations to expectant mothers. Pre-conception counseling offers information regarding the risks of pregnancy to both the mother and the fetus and should be delivered by practitioners with considerable experience in this area. It is imperative to assess baseline functional status and allow early referral to a cardiologist for medical optimization to better prepare for the difficulties that pregnancy, labor, and delivery pose to this unique population.

Reprint requests and correspondence: Dr. Kathleen Stergiopoulos, Department of Medicine, Division of Cardiovascular Disease, HSC T-16 080, Stony Brook University Medical Center, Stony Brook, New York 11974-8167. Email: kathleen.stergiopoulos@stonybrook.edu.

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Key Words: cardiomyopathy ■ dilated cardiomyopathy ■ hypertrophic cardiomyopathy ■ pregnancy.

Pregnancy in Patients With Pre-Existing Cardiomyopathies

Kathleen Stergiopoulos, Elaine Shiang, and Travis Bench

J. Am. Coll. Cardiol. 2011;58;337-350

doi:10.1016/j.jacc.2011.04.014

This information is current as of July 30, 2011

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