INTRODUCTION

Peripartum cardiomyopathy (PPCM) is a rare but serious complication of pregnancy with an incidence in published series of 1:1300 to 1:4000 live births (1). This disorder classically presents in the time interval from the last month of pregnancy until 6 months after delivery, with the majority of cases presenting in the early postpartum period (2). Other than the precipitating factor of pregnancy, PPCM is clinically identical to other forms of primary dilated cardiomyopathy (3, 4). Medical therapy is primarily the standard treatment of heart failure due to systolic dysfunction, however, its presentation in young women of childbearing age presents some unique challenges. In this lecture, we shall present briefly the current understanding of the pathogenesis of peripartum cardiomyopathy, medical management, and the potential future roles of investigative therapies.

PATHOGENESIS

As in other forms of primary dilated cardiomyopathy, the etiology remains uncertain, however, evidence points towards an inflammatory pathogenesis. The reported incidence of cellular myocarditis on endomyocardial biopsy varies from 9% to 78% (5, 6, 7, 8) and this wide variation is similar to that seen in idiopathic dilated cardiomyopathy (IDCM). Multiparity is a risk factor for the development of this disorder, suggesting that previous exposure to fetal or paternal antigen may elicit an abnormal myocardial inflammatory response.

The timing of presentation in the immediate postpartum period supports an autoimmune pathogenesis. Adaptive changes in the maternal immune system allows the fetal tolerance necessary for successful pregnancy and include the induction of suppressor cells (9, 10). These adaptive changes likely underlie the clinical observation that autoimmune disorders such as multiple sclerosis which affect women during their reproductive years typically have lower relapse rates during pregnancy itself, with a marked increase in the immediate postpartum period (11). The majority of cases of peripartum cardiomyopathy present in this same early postpartum period in which restoration of the maternal immune system results in an increase in autoimmune exacerbations in other disorders.

An alternative to the inflammatory theory is that of a latent cardiomyopathy brought to fruition by the hemodynamic stresses of pregnancy. Hypertension during pregnancy, and in particular pre-eclampsia, are both reported in a higher frequency of women with peripartum cardiomyopathy and do support that hemodynamic stresses may play a role. However, given the normal hemodynamic changes of pregnancy, most women with compromised cardiac function, such as valvular heart disease, present with symptoms of heart failure by the end of the second trimester, and the absence of cardiac symptoms in PPCM until the postpartum period argues against the "latent cardiomyopathy" theory.

PRESENTATION AND EVALUATION

Shortness of breath, orthopnea, and paroxysmal nocturnal dyspnea in the recent postpartum period are the most common presenting symptoms. Fatigue is also quite common. While this is frequently dismissed and attributed to the demands of caring for a new infant, women with prior pregnancies may note fatigue out of proportion to their previous postpartum experience. Chest discomfort is usually more characteristic of pulmonary congestion than angina. Peripheral edema is often a manifestation of volume overload, however, when associated with other signs of right heart failure and hepatic congestion may suggest more...
serious right ventricular involvement.

Persistence of pulmonary complaints frequently leads to chest x-ray evaluation, particularly in the postpartum period. The finding of interstitial or alveolar edema, occasionally with associated cardiomegaly, may lead to the initial diagnosis. Electrocardiogram findings are generally non-specific and include poor R-wave progression, intraventricular conduction delay, and non-specific ST and T-wave changes.

Laboratory evaluation usually reveals little or no elevation in creatinine kinase, or cardiac troponin. In women with acute heart failure and hemodynamic compromise, assessment of liver function tests, and renal function provides an assessment of an organ perfusion. In contrast to myocarditis, fever and leukocytosis is uncommon and when present should elicit a thorough evaluation for postpartum sepsis as an alternative diagnostic possibility.

Echocardiography remains an important tool for evaluation and follow-up for women with postpartum cardiomyopathy. The finding of a decrease in myocardial systolic dysfunction, as manifest by a decrease in left ventricular ejection fraction or fractional shortening is essential to the diagnosis. Left ventricular dilatation is also frequently evident, particularly in those women presenting late. Mild compensatory left ventricular hypertrophy can be seen, however, marked increases in LV wall thickness may suggest primary hypertrophic cardiomyopathy, an entity with a very distinct natural history and prognosis. A small pericardial effusion may be seen in the early and presumably more inflammatory immediate postpartum period. Valvular morphology is generally normal, however, with marked LV enlargement mitral regurgitation secondary to annular dilatation may be seen. Overall, echocardiographic features of postpartum cardiomyopathy are indistinguishable from those of primary non-ischemic dilated cardiomyopathy.

Initial evaluation should rule out other potential causes of heart failure. The most common alternative diagnosis, occult valvular heart disease, can be effectively ruled out by transthoracic echocardiography. The finding of normal systolic function excludes postpartum cardiomyopathy and should lead to an evaluation for forms of high output failure such as anemia and thyrotoxicosis. Although ischemic heart disease is uncommon in this population, women with significant risk factors such as Type I diabetes should have at least a non-invasive assessment for coronary ischemia, and if questions persist should undergo angiography. In women with persistent heart failure, hemodynamic instability or evidence of an organ dysfunction, right heart catheterization to assess filling pressures and cardiac output should be considered. Although some tertiary centers do perform endomyocardial biopsy to assess for cellular inflammation, this finding is of limited prognostic value and as it generally does not change therapeutic recommendations, its use has markedly decreased in frequency in recent years.

PROGNOSIS: POTENTIAL FOR RECOVERY

While peripartum cardiomyopathy shares many features of other forms of non-ischemic dilated cardiomyopathy, an important distinction is that women with this disorder have a much higher rate of spontaneous recovery of left ventricular function. As many as 50% of women presenting with this disorder will normalize their ejection fraction during subsequent follow-up, (12) most within the first six months. This higher rate of spontaneous recovery compared to other forms of IDCIM likely reflects differences in timing, not in pathogenesis. Patients presenting with idiopathic dilated cardiomyopathy may do so months to years after the initial myocardial injury, long after the time for spontaneous recovery has past. In contrast, for women presenting with peripartum cardiomyopathy, the timing of the initiating event is clear. As women present in the acute phase of the illness, there is a greater chance of spontaneous recovery once the hemodynamic or "inflammatory" stress of pregnancy resolves.

Prognosis is directly correlated to recovery of left ventricular function. For those women whose LVEF normalizes during follow-up their prognosis is excellent as without the stimulus of a subsequent pregnancy the chance of development of heart failure or future LV dysfunction is minimal. For those women whose left ventricular function does not recover, prognosis remains guarded and mortality rates as high as 10-
Few clinical clues exist which help predict which women will recover their LV function. Our experience suggests that LV size is an important predictor, as women presenting without significant LV dilatation appeared to have a greater chance of spontaneous recovery during follow-up. In contrast, women with marked LV dilatation at presentation appeared to have a greater likelihood of developing into a chronic cardiomyopathy. Initial NYHA class or hemodynamics do not seem to predict the likelihood of subsequent recovery. Women who remain severely functionally limited or inotrope dependent despite therapy should be evaluated for possible cardiac transplantation, however, we attempt to delay transplantation if possible for the first six months postpartum in the hopes that some recovery of LV function will allow transplant to be deferred.

**MEDICAL MANAGEMENT**

The medical management of peripartum cardiomyopathy is similar to other forms of heart failure due to systolic dysfunction with the exception that in women presenting during pregnancy, potential effects to the fetus must be considered (15,16). Therapy with angiotensin converting enzyme inhibitor are the core of therapy of women postpartum, but are contraindicated during pregnancy itself due to potential teratogenic effects ACE inhibitor use during pregnancy, particularly in the second and third trimester, has been associated with increased fetal loss and a fetopathy characterized by fetal hypotension, oligohydramnios-anuria and renal tubular dysplasia. Angiotensin receptor antagonist (ARB's) while a reasonable alternative to ACE inhibitor therapies postpartum, should be similarly avoided during pregnancy due to potential adverse effects.

For women presenting during pregnancy with symptoms of congestion due to cardiomyopathy, a loop diuretic can be utilized generally at the lowest effective dose. A small daily dose of digoxin can be added. In terms of afterload reduction, hydralazine and nitrates can be used as an alternative. Despite the growing evidence of the effectiveness of beta receptor antagonist (beta blockers) as heart failure therapy, less is known about their effectiveness for PPCM and their use must be individualized. In terms of safety, there is a long history of the use of beta blocker therapy in treating pregnant women with hypertension without any known adverse effects to the developing fetus, and for patients on these agents prior to diagnosis, they can be safely continued.

For patients presenting postpartum, ACE inhibitor therapy should be initiated. In those patients not tolerating ACE inhibitors due to cough, ARB's are an acceptable alternative. Symptoms of congestion should be treated with a loop diuretic and digoxin. For patients who remain symptomatic despite ACE inhibitor and diuretic therapy, beta blocker therapy can be initiated. These should be used with caution in the occasional acute patient who presents with significant systolic dysfunction without ventricular enlargement. These patients with normal LV chamber size have a markedly reduced stroke volume, and occasionally the reductions in heart rate associated with beta blocker therapy are poorly tolerated.

Like other forms of heart failure, this syndrome can lead to thrombotic and embolic complications. Patients with evidence of a systemic embolus, or with severe left ventricular dysfunction and documented mural thrombus, anticoagulation should be considered. Warfarin therapy is contraindicated during pregnancy and for women requiring anticoagulation, heparin must be utilized. Postpartum, in patients with either a clinical embolic event or with ultrasound evident of thrombus formation, Warfarin therapy should be utilized for a period of six months. The need for chronic anticoagulation should then be reassessed depending on the state of LV recovery.

As in other forms of non-ischemic dilated cardiomyopathy, ventricular arrhythmias can be an important clinical issue. Patients presenting with sudden death or ventricular tachycardia with hemodynamic compromise, strong consideration of an ICD is warranted due to the potential for a fatal recurrence. For patients presenting with symptomatic ventricular tachyarrhythmia which are hemodynamically well tolerated, management can be tempered somewhat by the potential transient nature of the myopathy and
amiodarone therapy at 200 to 400 mg po qd is an alternative. If left ventricular function recovers, the risk of serious arrhythmic event is markedly diminished and amiodarone therapy can be discontinued. For patients with asymptomatic non-sustained ventricular tachyarrhythmia we would not initiate amiodarone therapy, but would focus on correction of metabolic abnormalities and consider the addition of a beta receptor antagonist if not already being utilized.

ACTIVITY AND FOLLOW-UP

Although patients are encouraged to remain as active as their functional status allows, aerobic activities and heavy lifting are discouraged for at least the first six months postpartum while assessing the degree of left ventricular recovery. Given the metabolic demands of lactation, breast feeding is strongly discouraged in more symptomatically limited patients. As pharmacologic therapy to the patient can be passed on to the child in breast milk, we also discourage breast feeding in more functional patients, though this could be considered with careful monitoring of the child.

In terms of the reassessment of LV function, the echocardiogram should be repeated at 6 months post delivery; for those patients with persistent cardiomyopathy beta blockers should be added at this point if not already on therapy.

SPECIAL CONSIDERATIONS - HEMODYNAMIC STRESS OF DELIVERY

For patients presenting during the late stages of pregnancy, consideration should be given to limiting the hemodynamic stress of the delivery. Compensated patients may undergo vaginal delivery with appropriate monitoring. For those patients late in pregnancy with more significant hemodynamic compromise, consideration should be given to elective caesarian with invasive hemodynamic monitoring of the mother.

RISKS OF SUBSEQUENT PREGNANCIES

For patients whose left ventricular function fails to normalize during follow-up, subsequent pregnancies carries a high risk of left ventricular deterioration and progressive heart failure, and is strongly discouraged given the possible risk to the life of the mother. A more difficult question is the risk of subsequent pregnancy in women whose left ventricular function normalized. A recent large retrospective survey suggests that in women with normal ejection fractions at the time of subsequent pregnancy, there was an approximate 21% risk of the development of heart failure (6 of 28), and a drop in the mean ejection fraction from 0.56 to 0.49 (17). However, no serious complications were noted and the majority of those women had a successful delivery at term. This was in marked contrast to the women with persistent LV dysfunction prior to pregnancy in whom 3 deaths out of 16 women (19%) were noted, two occurring soon after delivery and one two years later. Overall, our recommendation is that pregnancy clearly be avoided in women with persistent left ventricular function. Women whose LV function normalizes should still be made aware of the risk of possible recurrence, though in the majority of these women successful pregnancy can be accomplished with appropriate monitoring.

IMMUNE MODULATORY THERAPY

Given the inflammatory nature of peripartum cardiomyopathy and the occasional appearance of myocarditis on endomyocardial biopsy, immunosuppressive and immune modulatory therapy have been utilized. Medei et al. reported on a series of 18 patients from Johns Hopkins in whom myocarditis was found in 78% and immunosuppressive therapy with prednisone and azathioprine was associated with resolution in 9 of 10 treated patients (7). In a similar fashion, we reported that immune modulatory therapy with high dose intravenous immune globulin (2 gm/kg) in a series of 6 women (with and without myocarditis on biopsy) was associated with a marked improvement in left ventricular function (18). The clinical applicability of both these reports has to be viewed with caution given the absence of a prospective control group. A randomized trial of immunosuppressive therapy in a related population with myocarditis did not prove efficacy in the Myocarditis Treatment Trial, (19) and in a similar fashion therapy with immune globulin did not improve outcomes in a randomized trial of patients with acute cardiomyopathy (IMAC Trial) (20). Neither trial addressed the use of these agents in peripartum cardiomyopathy. In general, given the high spontaneous recovery rate on conventional therapy, we advise against therapy
with either immune globulin or immunosuppression until one assesses how the patient will recover functionally on conventional medical therapy. For patients whose clinical status continues to deteriorate despite maximal medical therapy, alternative therapies including immune modulatory therapy may be considered.

THE FUTURE

Peripartum cardiomyopathy remains a rare but troubling complication of pregnancy. Current recommended therapy remains the standard pharmacologic treatment for heart failure due to systolic dysfunction, however, outcomes on conventional therapy vary widely. For up to 50% of women marked recovery of ventricular function will be seen during follow-up and standard therapy is all that is needed. However, for the remainder, chronic cardiomyopathy will persist. Future investigations must focus first on clinical and biological predictors of outcomes so that investigative therapy may be targeted to those women predicted not to recover. Given the rarity of this disorder, collaborative international multicenter studies will be of great assistance in the search to improve methodologies to diagnose and treat this troubling disorder.

REFERENCES
