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Review Article

PERIPARTUM CARDIOMYOPATHY: A CONDITION PHYSICIAN SHOULD BE AWARE OF!

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Introduction

Peripartum cardiomyopathy (PPCM) is a poorly characterized, rare form of cardiomyopathy. The etiology of PPCM is unknown, but viral, autoimmune, and idiopathic causes may contribute (1).Risk factors include multiparity, age>30 years, multiple pregnancies, obesity, hypertension, and toxemia.The presentation is similar to other forms of congestive heart failure. Signs and symptoms of PPCM resemble systolic heart failure, and it is diagnosed by exclusion. The diagnosis of PPCM should not be considered until other causes of cardiac dysfunction are ruled out. Echocardiography is central to diagnosis. An echocardiogram typically reveals an ejection fraction of <45% and/or fractional shortening of <30%, along with a left ventricular end-diastolic dimension>2.7 cm/m^2 of body surface area. (2) Treatment consists of diuretics, vasodilators, digoxin. Patients with PPCM are at high risk of thromboembolism, and therefore anticoagulation therapy should be considered. The prognosis is variable, ranging from complete recovery, to worsening heart failure requiring cardiac transplantation, or death. Future pregnancies are often discouraged because of the high mortality rate and risk of recurrence. Prognosis is related to recovery of ventricular function. (3, 4, 5).

Pathophysiology and Etiology

The exact cause of peripartum cardiomyopathy (PPCM) is unknown, but the usual causes of systolic dysfunction and pulmonary edema should be excluded. Many nutritional disorders have been suggested as causes, but other than salt overload, none has been validated by epidemiologic studies. An increased prevalence of myocarditis has been found in case series and in a small case-control study. Abnormal myocardial biopsy findings were associated with a worse long-term prognosis for recovery. More recent data have found a similar incidence of myocarditis in women with PPCM, compared to those with the idiopathic type. However, a study that found myocarditis in 62% of 44 women with

PPCM found that the finding did not correlate with survival (6).

Lower levels of selenium have been found in patients with PPCM. Autoantibodies against myocardial proteins have been identified in patients with PPCM but not in those with idiopathic cardiomyopathy (7).

Case reports and anecdotal experience have documented ejection fractions as low as 10-15% in patients with severe preeclampsia, with subsequent normalization of echocardiograms within 3-6 months. Preeclampsia has been listed as a risk factor, but it may be the cause in some cases. Noncardiogenic pulmonary edema has many causes, all of which must be considered. A study in 2005 found that 8 of 26 patients had parvovirus B19, human herpes virus 6, Epstein-Barr virus, and human cytomegalovirus detected after molecular analysis of myocardial biopsy specimens.(8, 9).

Clinical Findings

The clinical presentation of PPCM is most often dyspnea (90%), tachycardia (62%), and edema (60%) [10]. Some case studies also cite unusual presentations, including multiple thromboembolic events [11] and acute hypoxia [12]. Onset occurs one month prior to delivery and up to five months after delivery. However, the majority of women present postpartum. The most common clinical presentation (dyspnea, tachycardia, and edema) can be mistaken for another disorder, such as pneumonia or depression. Therefore, when a woman presents in the puerperium with these findings, an echocardiogram should be considered. Cardiac biomarkers, including B-type natriuretic peptide (BNP), are elevated in patients presenting with PPCM although these markers are not unique to PPCM. Elevations of troponin T (TnT) appear to have prognostic significance in this group. A Tnt0.04 ng/mL at presentation predicts persistence of systolic dysfunction with a sensitivity of 55% and specificity of 91% [13]. Inflammatory cytokines (IL-2, TNF and IL-6) are elevated in women with PPCM compared to pregnancy controls [14,15]. However, these cytokines are elevated in patients with other cardiomyopathies.ECG abnormalities are often noted on presentation, most commonly sinus tachycardia, nonspecific ST-T segment changes, LV hypertrophy, premature ventricular contractions, and bundle branch block [16].

Diagnosis

Patients with peripartum cardiomyopathy present with the typical signs and symptoms of left ventricular failure. The majority of cases occur after delivery and the immediate postpartum period. However, when the disease develops during the last month of pregnancy the diagnosis of cardiac failure is difficult to make by signs and symptoms alone since some of those symptoms, such as fatigue, orthopnea, and pedal edema, are common among normal parturients during late pregnancy. Further testing is required to establish the presence of cardiac failure. A chest x-ray consistently demonstrates cardiomegaly and pulmonary edema. Echocardiography confirms ventricular failure with increased left ventricular end-diastolic dimensions and decreased ejection fraction. Once cardiac failure is identified, peripartum cardiomyopathy must be differentiated from other disease processes that lead to heart failure, such as valvular heart disease. (17)

The echocardiography will rule out other valvular diseases and at the same time diagnose reduction in the left ventricular ejection fraction and dilatation of cardiac chambers. Most of the cardiologists would consider PPCM, if left ventricular ejection fraction less than 50% and in the presence of other two mentioned criteria for diagnosis of PPCM [see below]. Other nonspecific echocardiography findings in PPCM are left

atrial enlargement, mitral regurgitation and small pericardial effusion. The endomyocardial biopsy may show features of myocarditis, but the decision for biopsy should be taken after thorough discussion between patient and treating physicians. Viral and bacterial culture as well as coxasckie B titer should be considered in selected cases. Invasive hemodynamic monitoring will show elevated right and left heart filling pressures with low cardiac index. (18)

The National Heart, Lung and Blood Institute (NHLBI), with the National Institutes of Health (NIH), published diagnostic criteria for PPCM to direct more accurate research on epidemiology, pathophysiology, and outcomes. The criteria include: [1] onset of heart failure signs and symptoms in the last month of pregnancy or within 5 months postpartum; [2] LV systolic dysfunction with ejection fraction (EF) measured ≤45% or LV end diastolic dimension ≥2.7 cm/m^2; [3] no evidence of pre-existing heart disease prior to peripartum symptom onset; [4] no other identifiable causes of heart failure(19).

An objective measurement of LV function excludes women with normal cardiac function with postpartum volume overload, which is common due to normal physiologic changes of pregnancy. Finally, PPCM is a diagnosis of exclusion (20).

Invasive evaluation, such as cardiac catheterization or endomyocardial biopsy, is often unnecessary for diagnosis or treatment. The pathology identified on endomyocardial biopsy is often nonspecific edema, inflammation, hypertrophy, and fibrosis. Inflammation consistent with myocarditis is present in up to 50% of specimens (21, 22).

Who makes the diagnosis of PPCM?

Patients with PPCM most commonly present to gynecologists or primary care physicians. Where pneumonia is suspected a referral to a respiratory physician is often made. It would be desirable, however, for patients presenting postpartum with signs of cardiac failure such as shortness of breath, edema or general lassitude, or with peripheral emboli or cardiac arrhythmias, to receive an urgent echocardiogram to exclude PPCM (23).

Treatment

When considering tests or treatments in pregnancy, the welfare of the fetus is always considered along with that of the mother. Coordinated management with specialists (an obstetrician and maternal-fetal medicine team) is essential, with fetal heart monitoring. (24)

Angiotensin-converting enzyme (ACE) inhibitors and ARBs are contraindicated in pregnancy because they cause birth defects, although they are the main treatments for postpartum women with heart failure. The teratogenic effects occur particularly in the second and third trimester, with fetopathy characterized by fetal hypotension, oligohydramnios-anuria, and renal tubular dysplasia. (25) However, a recent study suggested a risk of malformations even after first trimester exposure to ACE inhibitors.(26)

Digoxin, beta-blockers, loop diuretics, and drugs that reduce after load such as hydralazine and nitrates have been proven to be safe and are the mainstays of medical therapy of heart failure during pregnancy. Beta-blockers have strong evidence of efficacy in patients with heart failure, but they have not been tested in peripartum cardiomyopathy. Nevertheless, beta-blockers have long been used in pregnant women with hypertension without any known adverse effects on the fetus, and patients taking these agents prior to diagnosis can continue to use them safely.

Heart failure treatment postpartum.

After delivery, the treatment is identical to that for nonpregnant women with dilated cardiomyopathy.

ACE inhibitors and ARBs**.** The target dose is one-half the maximum antihypertensive dose.

Diuretics are given for symptom relief.

Spironolactone or digoxin is used in patients who have New York Heart Association class III or IV symptoms. The goal with spironolactone is 25 mg/day after dosing of other drugs is maximized. The goal with digoxin is the lowest daily dose to obtain a detectable serum digoxin level, which should be kept at less than 1.0 ng/mL. In the Digitalis Investigation Group trial serum digoxin levels of 0.5 to 0.8 ng/mL (0.6–1.0 nmol/L) were most beneficial, and levels of 1.1 to 1.5 ng/mL (1.4–1.9 nmol/L) were associated with an increase in deaths related to heart failure.

Beta-blockers are recommended for peripartum cardiomyopathy, as they improve symptoms, ejection fraction, and survival. Nonselective beta-blockers such as carvedilol (Coreg) and selective ones such as metoprolol succinate (Toprol XL) have shown benefit. The goal dosage is carvedilol 25 mg twice a day (50 mg twice a day for larger patients) or metoprolol succinate 100 mg once a day. (27)

During pregnancy, the risk of thromboembolic complications increases due to higher concentrations of coagulation factors II, VII, VIII, and X, and of plasma fibrinogen. The risk may persist up to 6 weeks postpartum. Cases of arterial, venous, and cardiac thrombosis have been reported in women with peripartum cardiomyopathy, and the risk may be related to the degree of chamber enlargement and systolic dysfunction and the presence of atrial fibrillation.

Patients with evidence of systemic embolism, with severe left ventricular dysfunction or documented cardiac thrombosis, should receive anticoagulation. Anticoagulation should be continued until a return of normal left ventricular function is documented.

We await the results of the Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction trial, which should determine which drug will best prevent death or stroke in patients with ejection fractions of less than 35%.

Warfarin can cause spontaneous fetal cerebral hemorrhage in the second and third trimesters and therefore is generally contraindicated during pregnancy. However, guidelines from the American College of Cardiology and the American Heart Association on the management of patients with heart valve disease say that "warfarin is probably safe during the first 6 weeks of gestation, but there is a risk of embryopathy if the warfarin is taken between 6 and 12 weeks of gestation."The guidelines also say warfarin is "relatively safe" during the second and third trimesters but must be stopped and switched to a heparin several weeks before delivery. Unfractionated heparin or low-molecular-weight heparin can be used during pregnancy. However, should warfarin be needed for any reason, we believe a cesarean section should be performed to reduce the risk to the infant. (28)

Patients with severe heart failure despite maximal drug therapy need cardiac transplantation to survive and to improve their quality of life. However, fewer than 3,000 hearts are available for transplantation worldwide per year. Therefore, ventricular assist devices are indicated as a bridge to transplantation .Patients with symptomatic ventricular arrhythmias should be considered for defibrillator implantation.(29)

New treatments

Pentoxifylline improved outcomes, left ventricular function, and symptoms when added to conventional therapy in a small prospective study (30).

Intravenous immunoglobulin improved the ejection fraction in several studies and also markedly reduced the levels of inflammatory cytokines, namely thioredoxin. (31)

Immunosuppressive therapy does not yet have a fully proven role, but it could be considered in patients with proven myocarditis. Given the various etiologic mechanisms of peripartum cardiomyopathy, it is unlikely that immunosuppression will help all patients. Furthermore, without a large randomized trial, treatment successes may merely reflect the natural course of the disease.

Investigators have emphasized the need to rule out viral infection before starting immunosuppressive treatment, as the treatment may activate a latent virus, with subsequent deterioration in myocardial function.(32)

Bromocriptine (Parlodel). Peripartum cardiomyopathy develops in mice bred to have a cardiomyocyte-specific deletion of stat3, leading to enhanced expression and activity of cardiac cathepsin D and promoting the formation of a 16-kD proaptotic form of prolactin. Therefore, drugs that inhibit prolactin secretion may represent a novel therapy for peripartum cardiomyopathy. Based on this concept, two patients with peripartum cardiomyopathy were treated with bromocriptine, an inhibitor of prolactin secretion, and they showed a good recovery. We require large prospective randomized controlled studies to prove the beneficial effect of blocking prolactin in patients with peripartum cardiomyopathy. (33)

Prognosis

Recovery from peripartum cardiomyopathy is defined as recovery of LVEF to ≥0.50 or improvement by >0.20. As already mentioned, recovery usually occurs between 3 and 6 months postpartum, but might occur as late as 48 months postpartum (34). Delayed diagnosis, higher NYHA functional class, black ethnicity, LV thrombus, multiparity, and coexisting medical illnesses are associated with delayed recovery. In a 2-year, long-term follow-up study in 123 peripartum cardiomyopathy patients, mean LVEF increased from 0.28 to 0.46, and in just over half of these cases reached >0.50(35). Furthermore, recovery was greatest when baseline LVEF was >0.30 and impaired when baseline LV end-diastolic diameter (LVEDD) was >5.6 cm^5; patients exhibiting low levels of recovery often required a heart transplant. (36) Also, high troponin levels at baseline were predictive of poor LVEF at 6 months.(11) Inflammatory markers such as CRP correlate positively with baseline LVEDD and LVESD but negatively with LVEF in patients with peripartum cardiomyopathy.(37).

Even after complete recovery from peripartum cardiomyopathy, the risk of recurrence in subsequent pregnancies remains high, and LVEF, once improved, can worsen again. In a study of 44 women who recovered from peripartum cardiomyopathy and subsequently became pregnant, LVEF deterioration was more frequent in those with partial recovery than in those with complete recovery (44% vs 21%) (38, 39). In a prospective study of 61 post-peripartum cardiomyopathy pregnancies, relapse occurred more often in patients who had a prior LVEF <0.55 than in those who had a prior LVEF ≥0.55 (46% vs 17%) (40) Generally, post-peripartum cardiomyopathy pregnancies are marked by a decline in LVEF (41). Exercise stress echocardiography to estimate contractile reserve can uncover subtle residual cardiac dysfunction that might be exacerbated during a pregnancy (42) At present, it is difficult to predict outcomes of a post-peripartum cardiomyopathy pregnancy, and current peripartum cardiomyopathy

guidelines advise against future pregnancies (43).

Conclusion

Peripartum cardiomyopathy is a rare but serious condition of unknown cause that affects childbearing women. Diagnosis of peripartum cardiomyopathy requires heightened awareness among multidisciplinary patient care teams and a high degree of suspicion. Management of peripartum cardiomyopathy should aim first at improving heart-failure symptoms through conventional therapies, and then at administering targeted therapies. Targeted therapies (for example, intravenous immunoglobulin, pentoxifylline, and bromocriptine) show promise but need further clinical evaluation before they can be widely adopted. The prognosis is best when peripartum cardiomyopathy is diagnosed and treated early. Fortunately, despite a high risk of recurrence in subsequent pregnancies, many patients with peripartum cardiomyopathy recover within 3 to 6 months of disease onset. A large multicenter, prospective randomized trial is currently needed to evaluate the incidence, the pathophysiology (which would include setting up a bio-repository for genetic and translational studies), and the current therapies for peripartum cardiomyopathy.

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