Peripartum Cardiomyopathy

A Review

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Peripartum cardiomyopathy is idiopathic heart failure occurring in the absence of any determinable heart disease during the last month of pregnancy or the first 5 months postpartum. The incidence varies worldwide but is high in developing nations; the cause of the disease might be a combination of environmental and genetic factors. Diagnostic echocardiographic criteria include left ventricular ejection fraction <0.45 or M-mode fractional shortening <30% (or both) and end-diastolic dimension >2.7 cm/m². Electrocardiography, magnetic resonance imaging, endomyocardial biopsy, and cardiac catheterization aid in the diagnosis and management of peripartum cardiomyopathy. Cardiac protein assays can also be useful, as suggested by reports of high levels of NT-proBNP, cardiac troponin, tumor necrosis factor-α, interleukin-6, interferon-γ, and C-reactive protein in peripartum cardiomyopathy. The prevalence of mutations associated with familial dilated-cardiomyopathy genes in patients with peripartum cardiomyopathy suggests an overlap in the clinical spectrum of these 2 diseases.

*Treatment for peripartum cardiomyopathy includes conventional pharmacologic heart-failure therapies—principally diuretics, angiotensin-converting enzyme inhibitors, vasodilators, digoxin, β-blockers, anticoagulants, and peripartum cardiomyopathy-targeted therapies. Therapeutic decisions are influenced by drug-safety profiles during pregnancy and lactation. Mechanical support and transplantation might be necessary in severe cases. Targeted therapies (such as intravenous immunoglobulin, pentoxifylline, and bromocriptine) have shown promise in small trials but require further evaluation. Fortunately, despite a mortality rate of up to 10% and a high risk of relapse in subsequent pregnancies, many patients with peripartum cardiomyopathy recover within 3 to 6 months of disease onset. **(Tex Heart Inst J 2012;39(1):8-16)**

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Peripartum cardiomyopathy is a rare, serious disease of late pregnancy or early puerperium. In 1971, Demakis and colleagues[1] first defined peripartum cardiomyopathy as idiopathic heart failure (HF) occurring in the absence of any determinable heart disease in the last month of pregnancy or during the first 5 months postpartum. Later, to prevent over-reporting, echocardiographic criteria (Table I) were added to this definition.[2]

Peripartum cardiomyopathy is characterized by its rapid clinical course[3] and a probability for spontaneous recovery.[4] It is of interest that early and late presentations of heart failure in pregnancy appear to have similar demographics and outcomes,[5] for this suggests that the same disease process underlies the 2 presentations. This has led to a call to review the existing definition of peripartum cardiomyopathy to include patients who currently do not fit those strict criteria.[6]

Epidemiology

Data from population-based and single-center studies provide the best available estimates of the incidence of peripartum cardiomyopathy. The reported incidence fluctuates globally but is higher in developing countries. For example, the incidence in Nigeria[7] (1%) or Haiti[8] (0.33%) surpasses that in more developed countries, such as South Africa[9] (0.1%) or the United States (1:3,000–4,000 deliveries).[4] Environmental and genetic factors, differences in cultural practices, and standards of perinatal care may account for this regional disparity.

Cause

Specific causal factors for peripartum cardiomyopathy have not yet been identified. Black race,[10] multiparity,[11] maternal age >30 years,[12] twin pregnancies,[5] and history of hypertension, preeclampsia, and eclampsia are each associated with a higher incidence of peripartum cardiomyopathy, but no causal association has been shown. Recent evidence, though, suggests that inflammatory and genetic mechanisms are at work in peripartum cardiomyopathy.

Role of Inflammation in Peripartum Cardiomyopathy

Reports of high concentrations of tumor necrosis factor-α (TNFα), interferon-γ, interleukin-6, C-reactive protein (CRP), and Fas/apoptosis antigen 1 (Apo-1) in peripartum cardiomyopathy[13] suggest an underlying inflammatory process for the pathophysiologic development of peripartum cardiomyopathy. Physiologic changes during pregnancy usually boost maternal antioxidant defense mechanisms.[14] However, peripartum cardiomyopathy patients exhibit high levels of oxidative stress (for example, increased levels of oxidized low-density lipoprotein).[3] In murine cardiomyocytes, deletion of the signal transducer and activator of transcription 3 (stat3) gene responsible for protection from oxidative stress causes peripartum cardiomyopathy in a dose-dependent fashion.[3] In brief, stat3 deletion leads to overexpression of cathepsin D, which cleaves prolactin into its 16-kDa active form, thereby enhancing the antiangiogenic and pro-apoptotic properties of prolactin that are so instrumental in destroying cardiac and vascular tissues.[3] Reports of elevated levels of Fas/Apo-1 at baseline predicting death in human beings support this hypothesis.[13]

Myocarditis

The existing literature indicates that most patients with peripartum cardiomyopathy have myocardial inflam-

TABLE I. Current Diagnostic Criteria for Peripartum Cardiomyopathy

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1. Development of heart failure in last month of pregnancy or 5 months postpartum
2. Absence of preexisting heart disease
3. Indeterminant cause
4. Echocardiographic findings (a, together with b or c; or all of these)
   a. Left ventricular end-diastolic dimension >2.7 cm/m²
   b. M-mode fractional shortening <30%
   c. Left ventricular ejection fraction <0.45

Adapted from Demakis JG, Rahimtoola SH. Peripartum cardiomyopathy. Circulation 1971;44(5):964-8[1]; and from Manolio TA, Baughman KL, Rodeheffer R, Pearson TA, Bristow JD, Michels VV, et al. Prevalence and etiology of idiopathic dilated cardiomyopathy (summary of a National Heart, Lung, and Blood Institute workshop). Am J Cardiol 1992;69(17):1458-66.[2]

mation. Accordingly, in this review, we use the term myocarditis to refer to that inflammation. We emphasize, however, that the cause of the inflammation remains obscure.

The lines of evidence for and against a role for myocarditis in the causation of peripartum cardiomyopathy are tenuous. On the one hand, cardiomyocyte necrosis after interstitial and perivascular inflammation was first identified in peripartum cardiomyopathy patients,[15] the reported incidence of myocarditis in peripartum cardiomyopathy ranges from 29% to 100%,[16] and at least 1 group has reported viral genomes in 31% of peripartum cardiomyopathy patients with interstitial inflammation.[17] On the other hand, the rates of myocarditis among peripartum cardiomyopathy patients are not universally high.[18,19] Why the reported rates of active myocarditis in peripartum cardiomyopathy vary so widely is unknown. Confounding factors may include the likelihood that endomyocardial biopsy detects myocarditis when it is performed closer to the onset of peripartum cardiomyopathy,[18] the absence of magnetic resonance imaging (MRI) guidance in some of the endomyocardial biopsy studies, the performance of endomyocardial biopsy at the wrong site, and the misdiagnosis of another type of heart failure as peripartum cardiomyopathy.[18,20]

Fetal Chimerism

Fetal cells escaping into the maternal circulation during pregnancy are generally destroyed by the maternal immune system.[21] However, some of these chimeric cells with weak paternal haplotype may somehow evade the weakened maternal immune system during pregnancy and settle in the maternal heart, where they reside until they trigger a postpartum response by the normalized immune system.[22] High titers of antibodies directed against cardiac myosin heavy chains have been identified in the sera of peripartum cardiomyopathy patients but not in patients with idiopathic dilated cardiomyopathy (DCM) or in healthy individuals.[21] This could explain the higher incidence of peripartum cardiomyopathy in twin pregnancies and recurrences in subsequent pregnancies.[16] Meanwhile, the causal relationship, if any, between these antibodies and peripartum cardiomyopathy remains unclear.

Genetic Associations

The prevalence of mutations associated with familial dilated cardiomyopathy genes in patients with peripartum cardiomyopathy suggests that there may be an overlap in the clinical spectrum of these two diseases. van Spaendonck-Zwarts and colleagues[23] identified 5 cases of peripartum cardiomyopathy among 90 cases of familial DCM. They also identified 3 patients with peripartum cardiomyopathy who had an incomplete recovery and had first-degree DCM relatives, including 1 patient who had a *c.149A>G, p.Gln50Arg* mutation. Other investi-

gators identified familial mutations in *MYH7*, *SCN5A*, and *PSEN2* genes and sporadic mutations in *MYH6* and *TNNT2* DCM genes of peripartum cardiomyopathy patients.[24] If these findings represent a true association between cardiac gene mutations and peripartum cardiomyopathy, they may pave the way to genetic screening tests for peripartum cardiomyopathy.

Clinical Presentation and Diagnosis

Typically, peripartum cardiomyopathy occurs in the first 4 months postpartum; fewer than 10% of cases occur prepartum.[6,25] Common symptoms include dyspnea, cough, orthopnea, hemoptysis, and paroxysmal nocturnal dyspnea. Most affected patients have New York Heart Association (NYHA) class III or IV function.[16] Additional symptoms include nonspecific fatigue, malaise, palpitations, chest and abdominal discomfort, and postural hypotension.[16] Diagnosis requires a high degree of suspicion, because symptoms of peripartum cardiomyopathy can be confused with physiologic changes associated with advanced pregnancy. Common signs of peripartum cardiomyopathy include displacement of the apical impulse, presence of S_3, and evidence of mitral or tricuspid regurgitation. Engorgement of the neck veins, pulmonary crepitations, hepatomegaly, and pedal edema may also be present.[16,25]

Peripartum cardiomyopathy is diagnosed only when the following criteria are met: left ventricular ejection fraction (LVEF) <0.45 or M-mode fractional shortening <30% (or both) and end-diastolic dimension >2.7 cm/m^2 (Table I).[2] The differential diagnosis includes accelerated hypertension, diastolic dysfunction, systemic infection, pulmonary embolus, and obstetric complications such as preeclampsia, eclampsia, and amniotic fluid embolism. Diagnosis and postpartum monitoring are facilitated by electrocardiography, echocardiography, MRI, endomyocardial biopsy, and cardiac protein assays.

Electrocardiography

No pathognomic changes in electrocardiograms have been identified for peripartum cardiomyopathy. The most commonly seen electrocardiographic changes are left ventricular (LV) hypertrophy and ST-T wave abnormalities.[26] Complications such as atrial fibrillation and flutter, Q waves in anteroseptal leads, prolonged PR and QRS intervals, and bundle branch blocks are also seen.

Doppler Echocardiography

Echocardiography is essential for diagnosis (Table I). Its effectiveness obviates the need for invasive cardiac catheterization.[16] Common echocardiographic findings include globally decreased contractility and LV enlargement without hypertrophy.[25] Echocardiography is also useful for diagnosing mural thrombus, mitral or tricuspid regurgitation, and pericardial effusion.[6] Follow-up

studies have revealed that higher LVEF at presentation portends better cure rates and shorter recovery times.[27] Moreover, patients with high initial LVEF are less likely to experience relapse during a subsequent pregnancy.[28] Prompt echocardiography in all symptomatic pregnant patients can help to reveal patients with undiagnosed peripartum cardiomyopathy earlier in the course of the disease, thereby leading to earlier institution of care and to improvement of outcomes. Dobutamine stress echocardiography can determine the contractile reserve of patients with a history of peripartum cardiomyopathy and can help identify those at risk of relapse.[28] Follow-up echocardiography to monitor progress should be done at discharge from the hospital, at 6 weeks and 6 months postpartum, and annually thereafter.[6]

Magnetic Resonance Imaging

Cardiac MRI using T_2-weighted spin echo sequences enables the precise diagnosis of myocarditis, necrosis, and LV thrombi, and it yields accurate measurements of ventricular volumes. In addition, MRI helps identify endomyocardial biopsy sites. Injection of gadolinium as the contrast agent is best avoided prepartum, because gadolinium can cross the placenta.[29,30]

Endomyocardial Biopsy

Endomyocardial biopsy is a highly specific technique for diagnosing myocarditis.[31] However, its invasive nature, coupled with the varying incidence of myocarditis in peripartum cardiomyopathy, precludes its use as a first-line diagnostic tool.[16] Biopsy under MRI guidance improves accuracy and can be followed up with polymerase chain reaction analysis of biopsy DNA extracts for viral assays or immunohistochemical staining for autoantibody assays. Endomyocardial biopsy might be considered when myocarditis is strongly suspected or no improvement is seen after 2 weeks of heart-failure therapy.[16]

Cardiac Protein Assays

Cardiac protein assays show promise for diagnosis and postpartum disease monitoring. In one series of 38 patients,[32] N-terminal proBNP (NT-proBNP) levels were significantly higher in peripartum cardiomyopathy patients than in healthy postpartum control participants (P <0.0001). In a larger prospective trial of 106 patients,[33] high cardiac troponin T levels (>0.4 ng/mL) within 2 weeks of peripartum cardiomyopathy onset significantly predicted smaller LVEF and persistent LV dysfunction at 6-month follow-up (P <0.001). Although cardiac protein assays are not yet part of the standard management protocol for peripartum cardiomyopathy, their clinical usefulness continues to be evaluated.

Other Tests

Cardiac catheterization has been superseded by noninvasive imaging techniques. It is, however, still needed

to perform endomyocardial biopsies, and to evaluate the hemodynamic profile when noninvasive techniques may not be accurate.[16]

Management

Heart Failure Therapy

Because of its setting in the peripartum period, peripartum cardiomyopathy requires a well-coordinated multidisciplinary approach to management that involves cardiovascular medicine, obstetrics, immunology, pathology, and other specialties for the management of complications. The management of peripartum cardiomyopathy is similar to that of other types of heart failure. The first aim is to improve symptoms through conventional pharmacologic therapies and, if necessary, nonpharmacologic therapies. The second aim is to effect a cure through the administration of targeted therapies.

Oxygen, diuretics, and angiotensin-blocking drugs are used for the acute management of peripartum cardiomyopathy.[34] Regardless of the drugs used, their safety profiles during pregnancy or lactation must be considered (Table II), and their side effects must be closely monitored and managed.

Diuretics. Diuretics reduce preload and treat pulmonary congestion or peripheral edema. Both hydrochlorothiazide and furosemide are safe during pregnancy and lactation.[35] However, diuretic-induced dehydration can cause uterine hypoperfusion and maternal metabolic acidosis, so bicarbonate monitoring and management with acetazolamide are needed.[35] Potassium-sparing diuretic spironolactone has been used successfully to treat heart failure,[34] but the insufficiency of data regarding its use in pregnancy means that cautious administration is warranted.

Neurohormonal Blockade. Angiotensin-modulating agents are considered first-line drugs for heart-failure management. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers improve survival but are contraindicated in pregnancy.[34,36,37] Also, since they are secreted in breast milk, breastfeeding must be stopped before commencing therapy.[25]

Vasodilators. Hydralazine is safe during pregnancy and is the primary vasodilator drug antepartum.[25] More severe cases warrant the use of intravenous nitroglycerin starting at 10 to 20 µg/min and continuing up to 200 µg/min.[6] Nitroprusside is not recommended because of the potential for cyanide toxicity.[38]

Inotropic Agents. Use of inotropic agents such as dopamine, dobutamine, and milrinone is warranted only in cases of severe low output, and the patient should be weaned from them as soon as she is hemodynamically stable.[6]

Levosimendan reduces pulmonary capillary wedge pressure and improves cardiac output of peripartum cardiomyopathy patients.[39,40] In a randomized trial,

TABLE II. Safety Profile of Drugs during Pregnancy and Lactation

Drug Name	Class	
	During Pregnancy	During Lactation
Hydrochlorothiazide	B[a]	AAP-compatible
Furosemide	C[b]	Continue feeding
Lisinopril	D[c]	Discontinue feeding
Losartan	D	Discontinue feeding
Hydralazine	C	AAP-compatible
Nitroglycerin	C	Unknown/caution
Nitroprusside	C	Unknown
Dopamine	C	Unknown
Dobutamine	B	Unknown
Milrinone	C	Unknown/caution
Epinephrine	C	Unknown
Norepinephrine	C	Unknown
Digoxin	C	AAP-compatible
Metoprolol	C	AAP-compatible
Carvedilol	C	Discontinue feeding
Amlodipine	C	Not recommended
Quinidine	C	Continue feeding
Procainamide	C	AAP-compatible
Warfarin	X[d]	AAP-compatible
Enoxaparin	B	Caution
Intravenous immunoglobulin	C	Unknown
Pentoxifylline	C	Discontinue feeding
Bromocriptine	B	Discontinue feeding

AAP = American Academy of Pediatrics

[a]Class B: Animal reproduction studies have failed to show a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women; or animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.

[b]Class C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in human beings, but potential benefits may warrant use of the drug in pregnant women despite risks.

[c]Class D: Positive evidence of human fetal risk has been shown by adverse-reaction data from investigational or marketing experience or studies in human beings, but potential benefits may warrant use of the drug in pregnant women despite risks.

[d]Class X: Studies in animals or human beings have shown fetal abnormalities or there is positive evidence of human fetal risk on the basis of adverse-reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

however, 24 patients treated with levosimendan (0.1 µg/kg/min) for 24 hours (in addition to conventional therapy) showed no improvement.[41] Until adequate safety data are available, levosimendan should be avoided

antepartum and lactation should be held while using levosimendan. Since pregnant women are systemically vasoconstricted, vasopressors such as norepinephrine are usually avoided antepartum.

Digoxin. Digoxin, an inotropic and dromotropic agent, is safe to use during pregnancy.[42,43] The scarcity of available antepartum drug options and the increased hemodynamic loads during late pregnancy make digoxin an easy choice.

β-Blockers. β-Blockers are crucial for long-term management of systolic dysfunction.[34] Although safe during pregnancy, $β_1$-selective blockers are preferred over nonselective β-blockers to avoid anti-tocolytic action induced by $β_2$-receptor blockade.[44] Carvedilol combined with α blockade to restrict peripheral vasoconstriction has been shown to be effective in peripartum cardiomyopathy.[4,45] Patients receiving these drugs are weaned from them when ventricular function normalizes, within 6 to 12 months.

Calcium Channel Blockers. Dihydropyridines, such as amlodipine, have been shown to successfully reduce interleukin-6 levels in heart-failure patients,[46,47] but concomitant uterine hypoperfusion requires cautious use of these agents.[46]

Arrhythmia Management

Atrial fibrillation is the most common arrhythmia in patients with peripartum cardiomyopathy.[48] Quinidine and procainamide are relatively safe to use in puerperium and are therefore considered first-line antiarrhythmics.[49] Digoxin can also be used as first-line therapy.[43] Refractory atrial fibrillation requires the placement of permanent pacemakers and implantable cardioverter-defibrillators.[6]

Anticoagulation

Heart failure[50] and pregnancy[51] are independent risk factors for thromboembolism. The administration of low-molecular-weight heparin (LMWH) antepartum or heparin/LMWH and warfarin postpartum is recommended when the LVEF is <0.30.[52,53] Unfortunately, warfarin is teratogenic and must be avoided antepartum.[53]

Currently, there is no clear consensus on the appropriate duration of heart-failure drug therapy and its prophylactic role in subsequent pregnancies. The optimal approach is to follow the patient over time and gradually taper the drug doses over 6 to 12 months, when there is clinical and echocardiographic evidence of recovery. Complications and coexisting illnesses may require prolonged therapeutic support.

Mechanical Circulatory Support and Transplantation

In severe cases of peripartum cardiomyopathy, mechanical circulatory support and even heart transplantation may be needed. Both intra-aortic balloon pumps and LV assist devices (LVADs) have been used as bridges to transplantation.[6,54] Peripartum cardiomyopathy has resolved in some patients so treated with LVADs.[55] Because peripartum cardiomyopathy can resolve within 3 to 6 months postpartum,[27] LVADs can also serve as a bridge to recovery in cases of fulminant peripartum cardiomyopathy. In recent years, bridging to recovery via prolonged circulatory support has helped to dramatically decrease the percentage of peripartum cardiomyopathy patients requiring transplantation, from 33%[56] to 4%–7%.[5] Yet, few studies have looked into heart-transplant outcomes in peripartum cardiomyopathy patients and compared them with transplant outcomes in idiopathic DCM patients.[56-58] The potential for organ rejection in peripartum cardiomyopathy is high due to the increased prevalence of autoimmune mechanisms. Some investigators have suggested, interestingly, that transplantation at a younger age and closer to onset can improve prognosis.[25] Meanwhile, no data regarding the risk of rejection in subsequent pregnancies are available.[59]

Targeted Therapy

Immunosuppressive Drugs. Immunosuppressive drug therapy for peripartum cardiomyopathy has not been universally successful.[20,60] Empiric immunosuppressive therapy is not recommended because myocarditis is not present in all cases and because associated adverse events may occur.[20] However, it remains an option when active myocarditis has been confirmed by endomyocardial biopsy.[60]

Intravenous Immunoglobulin. Intravenous immunoglobulin therapy is a promising approach to improving cardiac function. In a small retrospective study of women with peripartum cardiomyopathy and an LVEF of <0.40, the improvement in patients treated with intravenous immunoglobulin was greater than in control participants (26% vs 13%, *P*=0.042).[61] These results, however, have not yet been replicated.[60]

Pentoxifylline. In a nonrandomized trial of peripartum cardiomyopathy, 29 patients were administered pentoxifylline 400 mg 3 times daily, while 30 control patients received standard care.[62] At 6 months, the pentoxifylline-treated group showed a clear survival benefit over the control group (1 death vs 8 deaths). This survival benefit was attributed to the TNF-α, CRP, and Fas/Apo-1 reducing actions of pentoxifylline.[62] Additional randomized trials to confirm these findings must be performed before broader clinical adoption.[62]

Bromocriptine. In a pilot study in peripartum cardiomyopathy, 10 patients were administered the prolactin inhibitor bromocriptine at a dose of 2.5 mg twice daily for 2 weeks and then 2.5 mg twice daily for 4 weeks, in addition to receiving standard care, while 10 control patients received only standard care.[6] The bromocriptine group had both better survival (1 vs 4 deaths) and

TABLE III. Major Studies That Have Investigated Prognosis in Peripartum Cardiomyopathy

Authors	Study Type	No. Pts.	Mean Age, yr	Enrollment Period	Mortality Rate, %	Findings
Karaye KM, et al.[65]	Cross-sectional	55	26	2008–2009	—	Peripartum cardiomyopathy associated with decreased QRS interval and decreased atrial arrhythmias. Mean age of peripartum cardiomyopathy lower than in other causes of cardiomyopathy.
Goland S, et al.[66]	Retrospective	182	29	2009*	28	Major adverse events are more common in nonwhites and with LVEF ≤0.25.
Gentry MB, et al.[10]	Retrospective	28	25	2003–2008	—	Black women had 15.7% higher relative risk of peripartum cardiomyopathy than nonblacks. Other risk factors include hypertension history, >2 previous pregnancies, and unmarried status.
Duran N, et al.[67]	Retrospective and prospective	33	33	1995–2007	30	LVEF >0.27 and LVESD ≤5.5 cm may predict LV recovery.
Safirstein JG, et al.[68]	Survey	55	32	2005–2007	—	Gestational hypertension positive, LVEF ≤0.35 at diagnosis, breastfeeding history, and postpartum diagnosis are associated with peripartum cardiomyopathy recovery.
Hasan JA, et al.[69]	Retrospective	32	32	2003–2007	—	Chronic hypertension, long-term tocolysis, pre-eclampsia, and multiple pregnancies were risk factors for peripartum cardiomyopathy.
Hu CL, et al.[33]	Prospective	106	28	2007*	—	LV dysfunction more persistent in pts with cardiac troponin levels >0.04 ng/mL.
Brar SS, et al.[70]	Retrospective	60	34	1996–2005	3.3	Peripartum cardiomyopathy incidence highest in black and lowest in Hispanic populations.
Sliwa K, et al.[71]	Prospective	80	30	2005*	10 (6 mo), 28 (2 yr)	Peripartum cardiomyopathy mortality rate remains high after 6 mo.
Sliwa K, et al.[13]	Prospective	100	32	2003–2005	15	C-reactive protein level correlated with LVEDD and LVESD and inversely with LVEF. High Fas/Apo-1 and low mean LVEF at presentation predicted death.
Fett JD, et al.[8]	Prospective	92	32	2000–2005	15	Mean LVEF and fractional shortening at diagnosis higher in recovered pts than in unrecovered pts.
Elkayam U, et al.[5]	Survey	100	31	2005	9	Subsequent pregnancy in peripartum cardiomyopathy pts is associated with decrease in LV function.
Isezuo SA and Abubakar SA[48]	Cross-sectional	65	28	2003–2005	12	Peripartum cardiomyopathy outcome influenced by cardiothoracic index, LVEF, and diastolic pressure. Patients who died had lower diastolic pressure and higher cardiothoracic index.
Modi KA, et al.[72]	Retrospective	44	25	1992–2003	16	In black pts, LV function and recovery rates comparable to those in studies reported from Haiti and South Africa.
Mielniczuk LM, et al.[73]	Retrospective	171	30	1990–2002	1.36–2.05	Peripartum cardiomyopathy pts more likely to be older, black, and with pregnancy-associated hypertensive disorder.
Fett JD, et al.[74]	Retrospective and prospective	47	32	1994–2001	14	Very high incidence of peripartum cardiomyopathy in Haiti (1 case/400 live births).
Chapa JB, et al.[75]	Retrospective	32	27	1988–2001	10	LV fractional shortening <20% and LVEDD ≥6 cm at diagnosis is associated with 3-fold risk of poor LV recovery.
Felker GM, et al.[76]	—	51	29	1983–1998	6	Patients with peripartum cardiomyopathy have better prognosis than do pts with other forms of cardiomyopathy.
Sliwa K, et al.[77]	Prospective	29	29	1996–1997	28	TNF-α, IL-6, and Fas/Apo-1 levels are elevated in peripartum cardiomyopathy pts. Fas/Apo-1 levels were higher in nonsurvivors.
Witlin AG, et al.[78]	Prospective	28	—	1986–1994	18	Commonly associated disorders included preeclampsia of chronic hypertension (19 pts), alcohol abuse (2), positive family history (2), and multiple tocolytic therapy (2).
Desai D, et al.[79]	Retrospective	99	29	1986–1989	14	Increasing age and multiparity did not favor adverse outcomes, but late presentation predicted adverse outcomes.
Carvalho A, et al.[80]	Prospective	19	26	1982–1988	16	Death is predicted by increased LVEDD and late onset of symptoms.

Fas/Apo-1 = Fas/apoptosis antigen 1; IL-6 = interleukin-6; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; Pts = patients; TNF-α = tumor necrosis factor-α

*Year in which recruitment began.

greater LVEF recovery (from 0.27 at baseline [both groups] to 0.58 [bromocriptine] vs 0.36 [control] at 6 mo).[63] Multicenter, randomized, blinded trials to confirm these findings and establish bromocriptine's safety profile in pregnancy must be performed before bromocriptine enters routine clinical use.[63]

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.[27] Delayed diagnosis,[64] higher NYHA functional class, black ethnicity,[10] LV thrombus,[64] multiparity,[11] 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.[5] 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.[64] Also, high troponin levels at baseline were predictive of poor LVEF at 6 months.[3] Inflammatory markers such as CRP correlate positively with baseline LVEDD and LVESD but negatively with LVEF in patients with peripartum cardiomyopathy[13] (Table III[5,8,10,13,33,48,65-80]).

The estimated mortality rate associated with peripartum cardiomyopathy in the United States is 6% to 10%.[81] Death usually occurs within 30 days but has occurred later as well.[11] The estimated 6-month and 2-year mortality rates in South Africa are 10% and 28%, respectively.[6] It is of interest that nonsurvivors have higher Fas/Apo-1 levels.[13]

Even after complete recovery from peripartum cardiomyopathy, the risk of recurrence in subsequent pregnancies remains high, and LVEF, once improved, can worsen again.[6] 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%).[82] 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%).[28] Generally, post-peripartum cardiomyopathy pregnancies are marked by a decline in LVEF.[83] Exercise stress echocardiography to estimate contractile reserve can uncover subtle residual cardiac dysfunction that might be exacerbated during a pregnancy.[28] At present, it is difficult to predict outcomes of a post-peripartum cardiomyopathy pregnancy, and current peripartum cardiomyopathy guidelines advise against future pregnancies.[6]

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 biorepository for genetic and translational studies), and the current therapies for peripartum cardiomyopathy.

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