

Peripartum Cardiomyopathy: Review of the Literature

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Peripartum cardiomyopathy (PPCM) is a rare but serious form of cardiac failure affecting women in the last months of pregnancy or early puerperium. Clinical presentation of PPCM is similar to that of systolic heart failure from any cause, and it can sometimes be complicated by a high incidence of thromboembolism. Prior to the availability of echocardiography, diagnosis was based only on clinical findings. Recently, inclusion of echocardiography has made diagnosis of PPCM easier and more accurate. Its etiopathogenesis is still poorly understood, but recent evidence supports inflammation, viral infection and autoimmunity as the leading causative hypotheses. Prompt recognition with institution of intensive treatment by a multidisciplinary team is a prerequisite for improved outcome. Conventional treatment consists of diuretics, β blockers, vasodilators, and sometimes digoxin and anticoagulants, usually in combination. In resistant cases, newer therapeutic modalities such as immunomodulation, immunoglobulin and immunosuppression may be considered. Cardiac transplantation may be necessary in patients not responding to conventional and newer therapeutic strategies. The role of the anesthesiologist is important in perioperative and intensive care management. Prognosis is highly related to reversal of ventricular dysfunction. Compared to historically higher mortality rates, recent reports describe better outcome, probably because of advances in medical care. Based on current information, future pregnancy is usually not recommended in patients who fail to recover heart function. This article aims to provide a comprehensive updated review of PPCM covering etiopathogenesis, clinical presentation and diagnosis, as well as pharmacological, perioperative and intensive care management and prognosis, while stressing areas that require further research.

Key Words: Cardiomyopathy, peripartum, obstetrics, complications, anesthesia

INTRODUCTION

Peripartum cardiomyopathy (PPCM) is a devastating form of cardiac failure affecting women mainly in their last months of pregnancy or early puerperium and often complicating their obstetrics as well as anesthetic management. Setting aside several historical expressions,¹⁻⁵ "peripartum cardiomyopathy" is now the term widely used to describe this clinical situation.^{1-3,6,7} In 1971, Demakis et al. first defined PPCM with three distinctive criteria (Table 1).^{1,2} The strict time limit used in their diagnostic criteria was intended to exclude congenital and acquired causes of heart failure that usually manifest by the second trimester.^{1,8} Even so, the occurrence of PPCM has been overestimated^{6,9,10} As a result, the PPCM workshop committee recommended the inclusion of echocardiographic features of left ventricular dysfunction to redefine PPCM.¹¹ Specific echocardiographic diagnostic criteria have been proposed (Table 2),¹² and their addition has resulted in easier differentiation between PPCM and other causes of cardiac failure.^{9,13}

Table 1. Diagnostic Criteria for PPCM

Diagnostic criteria for PPCM:

- Development of heart failure within last month of pregnancy or six month postpartum.
- Absence of any identifiable cause for heart failure.
- Absence of any recognizable heart disease before last month of pregnancy.

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Table 2. Additional Echocardiographic Diagnostic Criteria

Demonstrable echocardiographic criteria of left ventricular dysfunction:

- Ejection fraction < 45%
 - Left ventricular fractional shortening < 30%
 - Left ventricular end-diastolic dimension > 2.7 cm/m² body surface area.
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INCIDENCE

The incidence of PPCM varies worldwide.¹⁴ The first report of cardiac failure in pregnancy was made in 1849 by Ritchie,¹⁵ and it was commonly described as cardiomyopathy in the 1930s.^{4,16} Reported incidence of PPCM in non-African countries ranges between 1 : 3,000 to 1 : 15,000 live births.^{2,3,6,7,9,14,17} In South Africa, the reported incidence is higher (1 : 1,000 live births).¹⁸ A much higher incidence of 1 : 300 live births has been reported from Haiti,¹⁹ and an extremely high rate of 1% has been described in Nigeria.²⁰ Higher rates in developing countries may be due to variations in local cultural as well as puerperal practices, ecological factors, environmental influence, diagnostic criteria and reporting pattern used.^{3,20-23} Diagnosis based only on clinical features has also overestimated the incidence.^{1,6,9,10} A report from the United States of America (USA) revealed that PPCM is misdiagnosed in 50 - 75% cases.^{6,13,24} PPCM is estimated to make up less than 1% of pregnant mother-associated cardiovascular abnormalities.^{3,25} Overall, recent reports from various parts of the World show an incidence of 1 in 1,485 to 4,000 live births^{3,5,14,17,21,26-28} and the trend is increasing.^{5,11,28}

RISK FACTORS

Common reported risk factors for PPCM are advanced maternal age, multiparity, multiple gestations, black race, obesity, malnutrition, gestational hypertension, preeclampsia, poor antenatal care, breast feeding, cesarean section, alcohol, cocaine and tobacco abuse, low socioeconomic condition and family history.^{1-11,13,14,17-35} PPCM has been reported mostly in women older than 30

years,^{1-3,8,14,17,18,29,32,34,36,37} but it may occur in various age groups.^{2,13,27,29,35,36,38-43,44} Though PPCM has been reported in primigravida,^{1,2,8,18,19,27,29-31,38-42,45} it is found to occur more commonly with multiparity.^{1-3,6,8,14,17,19,24,25,28,29,34} In the USA the majority of afflicted Americans are of African Americans,^{1-4,7,14,17,20,24,25,35} though, Asian (Korean, Japanese, Chinese and Indians), Hispanic and Caucasians mothers have also been affected with PPCM.^{2,3,9,17,25,29,39} Twin pregnancy appears to cause a higher risk of developing PPCM.^{1-9,21-23,26-29} The reason for the association of PPCM with higher age, parity, multiple gestation and black race is not fully understood.⁵ Recently, it has occurred increasingly in younger, primigravida and white mothers.^{8,9,14,19,21,25,27,29,38,44,46} Higher age and parity are also becoming less distinct predisposing factors for the development of PPCM.^{19,31,34,35}

Reports of PPCM are available from tropical and subtropical regions,^{4,18,20} and the increased heat, humidity, high salt and fluid intake and the associated hypertension, local puerperal practices and lack of modern diagnostic facilities may be responsible for the observed extremely high incidence.^{3,14,20,21,23,26} Typical etiological nature points towards hypertensive heart failure caused by fluid overload rather than a true variety of PPCM.¹⁴ Preeclampsia and hypertension have been associated with a significant number of PPCM cases.^{1-6,9,14,16-18,20,25,27,29,35,44} Many authors even report it as a variety of hypertensive heart failure.^{4,6,19,46} However, preeclampsia alone rarely leads to heart failure in healthy women.^{6,17,29} Absence of vascular changes and disappearance of hypertension and preeclampsia before the onset of heart failure indicate that hypertension likely is merely associated with and aggravates PPCM, rather than playing an etiologic role.^{2,3} In contrast with the past, recent reports showing an association of hypertension and preeclampsia with PPCM are less frequent.¹⁹

Malnutrition, low socioeconomic status, poor antenatal care and breast feeding are also mentioned as risk factors in earlier reports,^{1-4,9,22,24} but substantial correlations of these factors have not been found in further studies.^{2,3,5,8,14,23,25,45} There are also reports of other rare risk factors such as maternal cocaine, alcohol and tobacco

abuse.^{6,9,10,17,35} PPCM also does not have a strong hereditary association.^{3,7,11,17,25} The publications mentioning these risk factors are several years old and based on small numbers of patients with older diagnostic criteria, and so the true association of these risk factors with PPCM needs serious reevaluation.^{9,35}

ETIOLOGY

The actual etiology of PPCM is unknown.^{1-3,5,9,14,17,19-25,29,35,47} Several hypotheses like myocarditis, viral infection, autoimmune factors, inflammatory cytokines, abnormal hemodynamic response to physiological changes in pregnancy, prolonged tocolysis and selenium deficiency have been postulated.^{1-5,9-11,14,17,21-26,29,48-53}

Myocarditis

Myocarditis is defined as dense interstitial as well as perivascular inflammatory infiltration of lymphocytes and macrophages in the presence of myocyte necrosis with or without fibrosis.^{25,45} Melvin et al. published the first description of myocarditis in three patients with PPCM.⁴⁶ Reported incidences of myocarditis range between 29 to 100 percent.^{8,13,25,45,46,54} Midei et al. reported a 78% incidence of myocarditis in newly diagnosed PPCM patients.²⁵ Recently, idiopathic dilated cardiomyopathy (IDCM) (9.1%) has also been reported in PPCM.¹⁰ Ravikishore et al. did not find any evidence of myocarditis in 12 patients.³⁸ These discrepancies may be due to inclusion of patients outside the diagnostic criteria, problems associated with performance, timing and interpretation of endomyocardial biopsies (EMB), variability of histological criteria and focal changes seen due to vasopressor therapy.^{5,10,11,22,23,25,45} O'Connell et al. suggest that myocarditis may play an important role in causation of PPCM early on, and it may be missed if the biopsy is delayed.⁴⁵ Magnetic Resonance Imaging (MRI)-guided EMB from contrast-enhanced areas may provide more positive evidence of acute myocarditis in the early part of the disease.⁵⁵ Eosinophils known to have collagenolytic and cardiotoxic property are found in significant

numbers in PPCM patients.⁹ Many such patients develop myocarditis, implying a role for eosinophils in the development of myocarditis in PPCM.⁵⁶

Despite such supporting evidence, it has not been possible to establish a true causal relationship of myocarditis with PPCM and to delineate whether it is the cause of PPCM or a different entity occurring during pregnancy.^{14,25}

Inflammatory cytokines

Silwa et al., in a large study, found higher concentrations of inflammatory cytokines like tumor necrosis factor α (TNF α), C-reactive protein (CRP), Interleukin-6 (IL-6) and Fas/Apo-1 (a marker of apoptosis) in PPCM patients.^{30,31} CRP levels correlated inversely with left ventricular ejection fraction (LVEF) in their study. High TNF α concentration may lead to advanced ventricular remodeling through specific cardiac receptors, resulting in ventricular dysfunction.⁵⁷ Podewski et al. found a significantly higher level of signal transducer and activator of transcription-3 against the myocardium in dead pregnant mice presenting with heart failure and apoptosis.⁵¹ Findings from another murine study indicate that myocardial apoptosis might have a causative role in PPCM.⁵² Larger studies targeting these cytokines need to be conducted to establish their role in PPCM.

Viral infection

Viral infection has also been implicated as a cause of myocarditis.^{6,9,11,14,25,45,46,55,58,59} Depressed immunity during pregnancy may lead to viral infection.^{5,11,45} Increased susceptibility to viral myocarditis has been seen in pregnant mice.^{3,5,11,14,45} Bultmann et al. found viral genomic material in biopsy specimens of PPCM patients.⁵⁸ Polymerase chain reaction (PCR) and extraction of genomic material from contrast MRI-guided EMB may help in successful detection of viral genomes.⁵⁵ At the same time, there are several reports without any prevalence of viral infection in PPCM patients,^{2,8,25,46,48,60} and it has been argued that viral cardiomyopathy should not be included in PPCM criteria.³ Specific further study is essential to

establish the relationship of viral myocarditis and PPCM.

Autoimmune factors

In the 1970s, several reports in support of an autoimmune nature of PPCM joined reports of fetal chimerism (presence of fetal cells in maternal circulation during and after pregnancy).^{3,11,25,46,50,61} It has been hypothesized that fetal cells belonging to the paternal haplotype escape into maternal circulation due to the depressed immune condition of pregnancy, and may remain in circulation for a long time without rejection. Such cells would be recognized as foreign antigens after normalization of maternal immunity following delivery and may trigger an immune response.¹¹ McMullan et al. have proposed that autoantibodies may be formed against the uterus, placenta or fetus in pregnant patients.⁶² Ansari et al. describe the presence of higher levels of male chromosomal DNA in patients with PPCM than in controls. Smaller concentrations of nonmaternal fetal cells may aid the viability of the fetus, but higher levels may trigger autoimmune disease.⁵⁰ Development of autoantibodies against smooth and cardiac muscle has also been reported.^{5,50} These autoantibodies may cross react with the myocardium and can cause cardiomyopathy.^{5,25,50,62} The higher rate of PPCM in twin pregnancies and its familial predisposition also support this autoimmune theory.³² Warraich et al. found markedly increased levels of immunoglobulin (IgG and subclasses) in PPCM patients. Higher IgG subclass 3 level was seen to be associated with higher NYHA (New York Heart Association) class symptomatic presentation.⁶³ Larger studies are needed to comment on the definitive role of autoimmunity in PPCM.⁸

Abnormal hemodynamic response to physiological changes in pregnancy

Blood volume and cardiac output (CO) increase, while systemic vascular resistance (SVR) decreases in pregnancy.^{3,9,14,26,64} Transient left ventricular dilatation may occur in response to this increased load.¹⁴ Reduction of left ventricular function in advanced pregnancy and early puerperium is

typically seen.⁶⁴ It has been postulated that PPCM may be an exacerbation of this normal phenomenon.¹¹

Selenium deficiency

Keshan disease, a form of dilated cardiomyopathy, has been reported to be associated with selenium deficiency.^{48,65,66} Cenac et al. found significantly low selenium concentrations in PPCM patients,⁴⁹ which might be a mere incidental association rather than a cause. Levander stated that selenium deficiency leads to increased susceptibility to viral infection, which may in turn cause cardiomyopathy.⁶⁶ Selenium supplementation has been shown to improve cardiac dysfunction in chronic tube-fed patients, stressing its importance in malnourished PPCM patients.^{65,67} However, Fett et al. did not find any such significance of selenium concentration in PPCM patients.⁵³

Other factors

Some less important factors which may contribute to the development of PPCM are:

Prolonged tocolytic therapy^{17,29,68}

However, this treatment may actually unmask existing heart disease rather than play an etiologic role.^{23,69}

Hormones

Relaxin, primarily an ovarian hormone, may cause excessive cardiac dilatation leading to cardiomyopathy.^{23,70} Although previously implicated, subsequent reports do not support any etiological role of estrogen, progesterone or prolactin in PPCM.^{3,9,14}

*Persistent Chlamydia Pneumoni infection*⁷¹

Among so many propositions, no study has clearly delineated any definitive factor(s) responsible for PPCM. Although the etiology is multifactorial,^{9,21,25,65,72} evidence supports myocarditis, inflammatory cytokines and autoimmunity as the leading mechanisms behind PPCM.^{3,5,9,11,21-23,29,64,69} Rarity and wide geographical variation make it more difficult to find out the actual cause.

PATHOLOGICAL FEATURES

Heart specimens appear pale, soft, dilated and heavier in PPCM.^{1-3,9,14} Mural thrombi are invariably seen in one or more cardiac chambers in patients with persistent ventricular dysfunction. Gray-white patches of endocardial thickening are often seen at the sites of mural thrombi.^{1-3,9,14} Cardiac valves and coronary vessels appear normal with the occasional presence of pericardial effusion.^{1,4,9,14} Histological evidence of hypertrophy, degeneration, fibrosis, interstitial edema, fatty and mononuclear cell infiltration is seen in the myocardium with a sparse to abundant collection of eosinophils.^{1-4,8-10,14,45} Electron microscopy has revealed varying degrees of enlargement, destruction or fragmentation of myofibrils, an increase in size and number of mitochondria, glycogen and some abnormal pertinacious material deposits.^{1-3,45,60} Histochemical pictures of myocardial cells denote occasional sarcoplasmic fat vacuoles containing triglycerides without any accumulation of lipofuscin or amyloid.³ Significantly low levels of plasma albumin, prealbumin, selenium and zinc have also been reported.^{22,49}

CLINICAL PRESENTATION

Symptoms

Dyspnea on exertion, cough, orthopnea and paroxysmal nocturnal dyspnea are commonly seen in patients with PPCM and often mimic left ventricular failure (LVF).^{1-3,9,14,17,18,21,22,30,34,36} Cardiac thrombus formations are not uncommon and they may present with embolic features like chest pain, hemoptysis and hemiplegia.^{1-3,9,14,17,21-23,27,28,34,35,37} Though extremely rare, single or multiple coronary embolisms (and myocardial infarctions) have taken place in patients with PPCM.^{73,74} Nonspecific symptoms like palpitations, fatigue, malaise and abdominal pain may be present in 50% of cases.^{1-4,9,11,14,17,20-22,33} Most PPCM patients present in NYHA class III or IV,^{19-22,25,38} but the use of NYHA classification may not accurately reflect severity because of the normal occurrence of these features in advanced pregnancy.^{9,26}

Signs

Blood pressure may be normal, elevated or low.^{9,14} Tachycardia, gallop rhythm, engorged neck veins and pedal edema are commonly found^{1-4,9,11,14,17,20-22,33} Clinically, the heart may be normal or there may be mitral and/or tricuspid regurgitation with pulmonary crepitations and hepatomegaly.^{1-3,11,17,2} Patients may even present with seizures associated with cerebral edema and cerebellar herniation.^{17,21,39}

DIAGNOSIS

Diagnosis of PPCM is based on excluding common causes of cardiac failure such as infection, toxins and metabolic, ischemic or valvular heart disease.^{1-3,9,11,14,21,27} Early diagnosis of PPCM may be difficult because many of the similarities of its presenting features with that of advanced pregnancy.^{3,9,11,14,22,23,69} Complications of late pregnancy (like anemia, toxemia and amniotic fluid embolism) have similar manifestations that must be kept in mind.^{9,14} The commonest presentation of PPCM is in the postpartum period when most of these features are disappearing.^{1,8,9,14,17,29,44} Echocardiography and other laboratory evaluations strengthen the clinical diagnosis. Common differential diagnoses include accelerated hypertension, preeclampsia, IDC, pulmonary embolism, anemia and thyrotoxicosis, among others.^{6,9,14,17,22,69}

INVESTIGATIONS

Every patient should have an electrocardiogram (ECG), chest radiograph (CXR), and Doppler echocardiograph for diagnosis.^{9,22,26}

ECG

ECG usually shows sinus tachycardia, though there may be features of atrial flutter/fibrillation, left atrial and ventricular hypertrophy (LVH), left axis deviation, nonspecific ST-T abnormalities, low voltage complex, arrhythmia, Q wave in anteroseptal leads and conduction abnormalities like prolonged PR, QRS intervals and bundle

branch blocks.^{1-6,9,14,17,22,33,37-39,43,69} The occurrence of supraventricular/ventricular tachycardia, premature beats and features of myocardial infarction are also reported.^{1,14,23,39,42,43,45,74,75} The ECG may even be normal in many cases.^{5,14,17,22,45}

CXR

There may be evidence of cardiomegaly, LVH, pulmonary edema, pulmonary venous congestion and bilateral pleural effusion on CXR,^{1,2,7,9,14,17,37,39} or it may be normal.³

Doppler echocardiography

Doppler echocardiography is the most essential diagnostic tool for assessing the severity and gauging the prognosis of PPCM patients.^{11,22,69} Common echocardiographic features include increased left ventricular end diastolic diameter (LVEDD), decreased left ventricular fractional shortening (LVFS) and LVEF. Variable systolic wall thickening, B notch in M mode measurement, dilatation of all cardiac chambers, mitral, tricuspid, pulmonary and aortic regurgitation, diffuse wall motion abnormality and small pericardial effusions are also reported.^{9,11,14,17,20-22,27,29,32,33,36-42,46,68,69} These regurgitant murmurs are probably the consequence of cardiac dilatation.³² Patients with concomitant myocarditis have more systolic dysfunction than those without myocarditis.⁸ Elevated pulmonary artery pressure (PAP) and pulmonary arterial hypertension (PAH) are also seen in the majority of cases.^{27,37,42} Sometimes, right ventricular dysfunction and left atrial enlargement may also be present.^{32,42} In a significant number of cases, cardiac thrombi are found in different chambers.^{14,17,27,30,35} MRI is a more sensitive tool to diagnose such thrombi than echocardiography. Echocardiographic measurements have been used for prognostication of PPCM,^{9,11,14,17,19,29,35,38,45,54} but dobutamine stress echocardiography, having the capability to show the contractile reserve, may be a better tool in this regard.⁷⁶

Endomyocardial biopsy

The role of routine EMB in PPCM patients is controversial.^{13,25,65,9,10,17,45,77} The diagnostic sensitivity

of EMB is reported to be 50%, whereas specificity is very high (99%).³ EMB has a high rate of false negativity and results may vary with the timing of the biopsy. EMB in the early part of the disease process gives a better positive result.^{5,9,25,46} Raised levels of inflammatory cytokines and lymphocytic myocarditis should be considered more important than conventional Dallas criteria for myocarditis. Contrast MRI-guided EMB may provide more positive results. Interestingly, the majority of contrast enhancement due to myocarditis is seen in the lateral wall. PCR and immunohistological tests of EMB may be more helpful for detection of inflammation.⁵⁵ EMB always carry some procedural risk, and so it is best considered if the patient does not improve even after two weeks of conventional management.^{2,5,14,23,25,29,59} or there is a strong clinical suspicion of myocarditis.⁷³ However, it may be of value in diagnosis and screening of PPCM patients scheduled to undergo heart transplant and those coming for follow up after transplantation with features of rejection.^{13,78}

Cardiac catheterization

Cardiac catheterization is used for evaluation of left ventricular function, obtaining EMB and performing coronary angiography.^{8,9,13,22,27,38} It reveals elevated cardiac filling pressures and decreased CO and PAH,^{7,13,14,20,22,24,38,45,46} but its indications are limited to severe heart failure, abrupt deterioration of symptoms and associated ischemic heart disease (IHD).⁶⁵ Coronary angiography should always be considered in patients with positive clinical and ECG features of IHD, acute coronary syndrome, hyperlipidemia, history of smoking and diabetes mellitus.^{13,22,45,73,74}

Other less frequently used investigations

Polymerase chain reaction (PCR)

Used for detection of viral pathology in PPCM patients who are not improving with conventional treatment.^{21,55}

Compliment fixation tests

To detect infection by microorganisms.²

Blood culture

To rule out any infective cause.^{2,9}

Radionuclide ventriculography

This method has been used to assess cardiac function,^{8,14,22,25,41,45} but has the drawback of radiation exposure and is superseded by echocardiography.¹² It may be superior in detecting regional wall motion abnormalities in IHD patients.^{25,45}

Immunofluorescence and immunohistochemical staining

Sparsely used for staining of EMB specimens for detection of autoantibodies against myocardium.^{3,22,55}

Estimation of cardiac enzymes

Cardiac enzymes are found to be within normal limits in PPCM and so is coronary angiography.^{3,14}

Routine hematological, biochemical and serological tests

To rule out other common heart diseases.^{2,9,39} Elevated CRP and cytokines suggest inflammatory cardiomyopathy and their estimation should now be strongly considered.^{30,31,57} The cost-effectiveness of such tests should be judged on a case to case basis.

PPCM vs. IDCM

PPCM was initially suggested as a variety of occult IDCM manifesting in late pregnancy.^{1,17,22,72} Though PPCM is identical to IDCM in several ways,^{1-3,8,10,38,45} most researchers now accept PPCM as a distinct entity^{1-3,11,43} for the following reasons:

- (1) PPCM occurs at a younger age and is generally associated with better prognosis.^{1,2,6,8,13,27,29,35,43,45,47,54}
- (2) The incidence of PPCM is higher than IDCM.¹⁰
- (3) PPCM occurs mostly postpartum (78 - 93%),^{2,6,8,17,19,25,26,29,38,44,63} whereas IDCM usually manifests by the second trimester.^{64,79}
- (4) PPCM exclusively affects pregnant women and recurrent PPCM is seen to manifest again in the peripartum period.^{1,72}
- (5) Varying types of hemodynamic patterns are seen in PPCM compared to IDCM.^{30,34}
- (6) Unique sets of antigen and antibodies against myocardium are seen in PPCM compared to IDCM patients.^{11,14,50,63,72}
- (7) The incidence of myocarditis is higher in

PPCM than in IDCM.^{25,45,46}

- (8) Heart size returns to normal after delivery in a greater percentage of PPCM patients compared to IDCM.^{1-3,21,25,29,47}
- (9) Contrary to IDCM, PPCM may lead to rapid worsening of clinical condition.^{8,9,22,45}

COMPLICATIONS**Thromboembolism**

Thrombi often form in patients with LVEF < 35%^{5,21,30,35} and mortality rates of 30 - 50% have been reported to be due to thromboembolism.^{1,9,14,16,22,27,35} Systemic embolism leading to transient ischemic attack (TIA), hemiplegia, pulmonary embolism, acute myocardial infarction (AMI), mesenteric artery occlusion presenting as acute abdomen, infarction of kidney resulting in pyelonephritis and splenic infarction have been reported.^{2-4,17-19,21,23,27,28,34,35,37,73,74} Peripheral thromboembolism leading to limb ischemia and gangrene have also been reported.^{21,34}

Arrhythmias

Arrhythmias like sinus tachycardia, atrial and ventricular tachycardia, atrial flutter and fibrillation, ventricular premature beats, atrial and ventricular extra systoles and Wolfe-Parkinson-White Syndrome are reported in PPCM.^{2,33,39,42,74,80} Ventricular tachycardia leading to cardiac arrest has also taken place.³⁹ Increasing use of automated implantable cardioverter defibrillators (AICD) in PPCM patients supports the high risk of life-threatening arrhythmias.^{8,29}

Organ failure

Acute liver failure and hepatic coma arising from passive congestion of cardiac failure in a PPCM patient have been described.⁷³ Fatal bacteremia and multiorgan failure including the heart, liver and kidney have also been reported.^{29,39}

Obstetric & perinatal complications

Increased incidence of abortion (4 - 25%), pre-

mature delivery (11 - 50%), small for date and low birthweight babies, intrauterine growth retardation and fetal deaths are reported in PPCM.^{14,17,29,44} Congenital fetal anomalies are also described in a few cases (4 - 6%).²⁹ Congestive cardiac failure is associated with higher infant mortality (10%).³

MANAGEMENT

Medical management of PPCM is similar to that of heart failure.^{1,5,9,21,22,35,65} Fluid and salt restriction, digoxin, diuretics, vasodilators and anticoagulants are the mainstays of treatment.^{5,9,11,14,17,21-23,26,27,35,65} ⁸¹ Safety in pregnancy and lactation should always be considered before selecting a drug.^{11,23}

Non-pharmacological measures

Strict bed rest of 6 - 12 months, as had been advocated previously, is associated with a lower incidence of cardiomegaly,²⁴ but the same results can be achieved without prolonged bed rest.¹ Bed rest may in fact predispose the patient to deep venous thrombosis, increasing the risk of subsequent pulmonary embolism.⁹ Once incapacitating symptoms resolve with medical management, modest exercise may actually improve muscles as well as arterial tone.^{1,11,22,65,82} Salt and fluid intake should be restricted to 2 - 4 gm/day and 2 L/day, respectively, and are also important in symptomatic improvement.^{3,5,23,65,81}

PHARMACOLOGICAL MANAGEMENT

Digoxin

Digoxin is beneficial for its inotropic and rate-reducing effect,^{9,21,22} and provides symptomatic relief without reducing the mortality rate.⁸¹ It is safe in low doses (higher dose may even increase inflammatory cytokines) during pregnancy and lactation and serum digoxin level should be monitored, particularly when it is co-administered with diuretics, as pregnant women are unduly sensitive.^{1,3,9,14,21,22,24,82} Continuing digoxin for 6 - 12 months may reduce the risk of recurrence of PPCM.¹⁴

Diuretics

Diuretics are safe in pregnancy and lactation.²¹⁻²³ These are indicated for preload reduction and symptomatic relief when salt restriction fails.^{9,21,22,69} However, precaution must be taken against iatrogenic dehydration causing uterine hypoperfusion resulting in fetal distress.^{5,21-23} A loop diuretic is commonly used in the hospital setting,^{6,36,37,40-42} but thiazides can be used in milder cases.^{34,81} Metabolic alkalosis may develop due to diuretic-induced dehydration. Addition of acetazolamide will cause reduction of alkalosis by removing bicarbonate.⁸¹ Spironolactone, probably due to aldosterone antagonism, has been seen to reduce symptoms, frequency of hospital admission and mortality in severe heart failure patients when used in combination with standard management.⁸³ However, spironolactone may not be safe in pregnancy and is better avoided in the antepartum period.^{65,81}

Vasodilators

Because of preload and afterload lowering effects, vasodilators are vital in heart failure management. They improve both CO and the outcome of the failing heart.^{5,9,14,22,26,65} Angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) are now considered a mainstay of management and have been shown to reduce mortality significantly in heart failure patients.^{5,9,22,23,27,65,82,84} They are contraindicated in pregnancy due to teratogenicity,^{9,21,22,43,65} but should definitely be considered after delivery, and can even be considered in advanced pregnancy when other drugs are ineffective.^{22,26} ACEI are excreted in breast milk and thus breastfeeding should be discontinued in patients requiring ACEI.⁹ Hydralazine with or without nitrates is generally the vasodilator of choice during pregnancy^{5,9,11,21-23,82} and has been shown to reduce mortality in the Veterans Administration Heart Failure Trial.⁸⁴ Infusion of nitroglycerin and sodium nitroprusside (SNP) may be needed in severe situations.^{5,22,23,32,36,37,40,41,78} Because of the concern of cyanide toxicity, SNP may not be a good choice in the antepartum period.^{5,23}

Calcium channel blockers

Initially, the use of calcium channel blockers (CCB) was not acceptable in heart failure because of their negative contractile effect and the potential risk of uterine hypoperfusion.^{9,11,23,69,85} Amlodipine has now been shown to improve survival in non-ischemic cardiomyopathy patients.⁸⁵ Amlodipine resulted in reduction of IL-6 in the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) trial, suggesting a potential role in PPCM management.⁸⁶ Levosimendan, a calcium sensitizer having vasodilatory properties, improves cardiac contractility in heart failure patients.^{23,40} Recently, it has been used in a PPCM patient, successfully causing a steady decline of elevated pulmonary capillary wedge pressure (PCWP) and subsequent improvement of CO.⁴⁰ Because of the lack of safety reports, breast feeding should be avoided in patients taking levosimendan.²³

Beta blockers

Like CCB, earlier beta blockers were also contraindicated in heart failure. Recent studies have documented their safety and efficacy in heart failure patients, though the survival rate is somewhat confusing.^{11,23,65,81} Beta blockers are not contraindicated in pregnancy, but their use is associated with low birth weight.^{5,23,83} Beta blockers with additional alpha blocking properties (example carvedilol) also reduce the afterload.¹¹ The reduction of mortality and hospitalization in chronic heart failure patients has been documented by the US Carvedilol Heart Failure Program.⁸⁷ Carvedilol has been safely used in pregnancy and PPCM.^{11,30} Beta blockers and ACEI may play an additional role in suppression of the immune response,²¹ and have also been shown to prevent remodeling and reduce ventricular dimensions.³⁵ There has been no consensus when to discontinue these primary drugs. Drugs can be gradually tapered over 6-12 months when ventricular function normalizes clinically and on echocardiography.^{21,35,45,81} If there is evidence of persistent cardiac dysfunction, associated hypertension or diabetes, drug therapy should be continued for a long period.^{35,65}

Antiarrhythmic agents

Antiarrhythmic agents may sometimes be required to treat symptomatic patients. No antiarrhythmic agent is completely safe in pregnancy. Non-pharmacological means like assurance, carotid massage or the Valsalva maneuver may be tried initially.⁸² Quinidine and Procainamide should be tried first because of their higher safety profile.⁸² Treatment should always start in a hospital setting because of the high incidence of torsades de pointes associated with their use. Beta blockers can also be used.^{30,82} Digoxin can be considered for atrial arrhythmias,⁶⁹ and adenosine can also be used in an emergency.³⁹ Amiodarone may cause hypothyroidism, growth retardation and perinatal death, so it should be avoided in the first trimester and reserved for life threatening arrhythmias only.^{43,69,82} Though primarily indicated in bradyarrhythmia, pacemakers have been used in PPCM patients for refractory arrhythmias.^{6,23,29,39,65,82} AICD can be considered in life threatening arrhythmias and has been shown to reduce the risk of sudden death in PPCM patients.^{11,29,82}

Anticoagulant therapy

Patients with an LVEF < 35% and bedridden patients with atrial fibrillation, mural thrombi, obesity and a history of thromboembolism benefit the most from anticoagulant therapy.^{1-3,5,9,11,14,17,21,23,30,35,65} The usual hypercoagulable state of pregnancy and stasis of blood due to ventricular dysfunction makes PPCM patients more prone to thrombus formation and subsequent complications.^{43,88} This situation may persist for as long as six weeks in the puerperium,^{9,35} necessitating the use of heparin in the antepartum and heparin or warfarin in the postpartum period.^{5,9,14,17,21-23,34,37,65,69,88} Warfarin is contraindicated in pregnancy for its teratogenic effect,⁸⁹ but the use of both heparin and warfarin is safe in lactation.^{9,23,88}

Immunosuppressive therapy

Immunosuppressive therapy with azathioprine and prednisolone has been tried in myocarditis-positive PPCM patients.^{3,8,25,45,46,59} Melvin et al.

first noted dramatic improvements in three patients with immunosuppressive therapy.⁴⁶ In another study, 9 of 10 patients showed improvement of PCWP and Left Ventricular Stroke Work Index (LVSWI) with prednisolone therapy.²⁵ However, the Myocarditis Treatment Trial failed to demonstrate any advantage of immunosuppressive therapy in PPCM patients.⁷⁷ Presently, there appears to be no indication for routine immunosuppressive therapy, but it can be considered in biopsy-proven PPCM patients who do not respond to standard medical management after two weeks.^{9,11,14,21-23,25}

Immunoglobulin therapy

Human intravenous immunoglobulin (IVIG) has been shown to improve ventricular dysfunction in six PPCM patients,⁸⁹ although it failed to show any advantage in IDCM patients.⁹⁰ Considering the increasing evidence of autoimmunity in PPCM, it may be prudent to consider IVIG in PPCM patients who do not respond to conventional treatment.^{65,89}

Interferon

Interferon has been used in biopsy-proven cases of viral myocarditis, resulting in improvement in echocardiographic parameters, however, it did not produce much symptomatic benefit in PPCM patients.⁵⁹

Immunomodulation

Pentoxifylline, an immunomodulating agent known to reduce production of TNF α , CRP and Fas/Apo-1, was recently shown to improve NYHA class, LVEF and outcome in 59 PPCM patients when combined with conventional treatment.^{30,31} More evidence is required before pentoxifylline can be recommended.

SURGICAL MANAGEMENT

Cardiac transplant is reserved for those who are resistant to all medical management.^{5,9,11,13,14,17,21-23,25,39,35,65,91} Success and survival rates are similar to

transplants performed in IDCM patients,^{11,17,22} but the rejection rate is greater due to high titers of circulating antibodies.^{11,17,22,65,91} Patients with young age, minimal end organ damage and recent onset PPCM have a more favorable outcome.^{9,91,92} Aggressive measures like intra aortic balloon pumps, ventricular assist devices or cardiopulmonary or venoatrial bypass may sometimes be needed as bridging measures until recovery of cardiac function or definitive cardiac transplant.^{5,35,38,39,65,92,93} Use of these techniques has led to complete recovery and rehabilitation,⁹³ but these aggressive measures are most useful for healthy young patients without features of myocarditis.^{9,78,92}

OBSTETRIC MANAGEMENT

PPCM during the antepartum period demands intensive fetal and maternal monitoring.²⁶ Though routinely not required, induction of delivery should be considered if a patient's condition deteriorates despite maximal medical management.^{14,23,26,29,37,65,69,81} A multidisciplinary approach involving an obstetrician, cardiologist, anesthesiologist and perinatologist may be required to provide optimal care to such patients.^{11,14,17,21-23,26,37,65,69,94} Regional analgesia reduces the cardiac stress of labor pain,^{14,22,26,42,69,95} while application of outlet forceps or a vacuum device can minimize the cardiac stress of the second stage of labor.^{22,23,26,64} Cesarean section has increased risk of blood loss, endometriosis and pulmonary embolism, and is best done for obstetric indications as well as in severe decompensated situations.^{5,14,17,22,23,26,29,35-37,64,69,94} Following delivery, these patients need monitoring in an Intensive Care Unit (ICU) for early detection and management of uterine autotransfusion-induced pulmonary edema.^{3,26,41,64,65,69} Obstetricians should counsel about breast feeding and future pregnancy at the time of discharge.¹⁴

Because of the high risk of thromboembolism with oral contraceptive pills (OCP), barrier contraceptive devices are better options for family planning.^{1,14,91} Surgical sterilization techniques like tubal ligation and vasectomy have also been used.^{3,9,26,32}

INTENSIVE CARE MANAGEMENT

Patients with severe forms of heart failure may require more aggressive management in an ICU with monitoring of arterial blood pressure (ABP), central venous pressure (CVP), a pulmonary artery catheter (PAC) and echocardiography along with inotrope, vasodilator and ventilator therapy.^{11,17,21-23,26,32,36-42,69,75,95} PAC use has a definite role in the ICU and perioperative management of severe cases,^{6,32,40,41} but its routine use is associated with many life threatening complications.⁹⁶ Echocardiography is a safer alternative.^{40,79,95} Inotropes like dopamine, dobutamine and noradrenalin are usually needed in hypotension.^{22,23,26,36,39,40,73} Inodilators such as amrinone, milrinone, enoximone and levosimendan may be needed in severe cases with high afterload.^{5,23,35,36,40,69,81} Vasodilatation with nitroglycerin, hydralazine or SNP can also be used in heart failure with high SVR.^{23,32,36,37,40,41,69} Levosimendan can be helpful in the weaning of ionotropes in ionotrope-dependent cases.^{23,40} Nesiritide, a brain natriuretic peptide (BNP), has been shown to reduce elevated PCWP and lead to clinical improvement, indicating its therapeutic role in PPCM.^{81,97} In extreme situations, multiorgan support like circulatory assist devices and continuous veno-venus hemodialysis may be instituted.^{35,37,40,65,93}

ANESTHETIC MANAGEMENT

The anesthesiologist plays a vital role in managing the patients in ICU, providing labor analgesia, optimizing medical condition of the mothers for cesarean section and administering anesthetics for urgent or elective cesarean section.

PREOPERATIVE OPTIMIZATION

This is mostly similar to ICU management.

Labor analgesia

Single-shot spinal anesthesia is currently not

preferred because of severe consequence like cardiac arrest and pulmonary edema.^{40,41} Controlled epidural analgesia (EA) under invasive monitoring is a safe and effective method.^{17,41} Sympathectomy induced afterload reduction by controlled regional analgesia has been shown to improve myocardial function in PPCM patients.^{42,69,79,94} Combined spinal-epidural (CSE) analgesia has the advantages of quick onset of spinal analgesia with short acting opioids and epidural catheter-driven prolonged analgesia with low concentrations of local anesthetics and opioids.⁷⁹ Continuous spinal analgesia (CSA) may be the safest alternative because of greater flexibility, drug dosage and quality of analgesia.^{32,79}

Anesthesia for cesarean section

Anesthetic management for cesarean section in PPCM patients can be challenging to anesthesiologists.³⁵⁻³⁷ Both general anesthesia (GA) and regional anesthesia (RA) have been used.^{32,36,37,39-42,75,94-96,98}

Regional anaesthesia

Though RA has the advantages of sympathetic blockade-induced preload and afterload reduction,^{42,69,79,94,95} spinal anesthesia is rarely used because of complications, as mentioned above. Graded EA has been mostly used because of its better hemodynamic stability.^{41,42,94,95} CSE, with its lower failure rates, faster onset, good muscle relaxation, postoperative analgesia facilities and better maintenance of hemodynamics has also been successfully applied.^{23,32,42} However, CSE may cause postdural puncture headache (PDPH), which can be largely avoided by the use of a finer gauge pencil point spinal needle.^{32,79} CSA may be considered in severe PPCM cases as it has the advantages of excellent analgesia, lesser drug requirement with rapid titrability and hemodynamic stability.^{23,32,42,79} However, CSA is associated with a higher incidence of PDPH and neurological complications, many of which can be avoided by using a macrocatheter and avoiding hyperbaric lidocaine.^{23,32,79} Recommended precautions should be taken while using RA in anticoagulated patients. Infiltration anesthesia with bilateral ilioinguinal nerve blocks has also

been used in a severely compromised patient.⁹⁸

General anesthesia

GA may be needed in emergency situations or when RA is contraindicated, particularly in anticoagulated patients. 36, 37, 41, 69, 75 GA has the advantages of airway control and ventilation, and it facilitates the use of transesophageal echocardiography.^{42,79} The stress of rapid sequence induction in compromised cardiac patients can be dangerous.⁴² Both inhalational and intravenous-based GA have been used in PPCM.^{36,37,41,75,96} GA can cause maternal and fetal cardiorespiratory depression.^{37,41,75} Severe bradycardia leading to cardiac arrest following institution of GA has been reported in PPCM patients.^{41,75} There is also increased risk of LVF and pulmonary edema.^{41,75} GA does not provide thromboprophylaxis like RA and carries a high risk of thromboembolism.³⁷ Opioid-based anesthesia may be advantageous in compromised cardiac conditions, but carries a high risk of fetal respiratory depression necessitating naloxone and artificial ventilation following childbirth.^{36,37,96} Vasodilators may be needed to accommodate extra blood released by uterine contraction after delivery.³² Invasive monitoring like ABP, CVP and PAC is recommended during anesthesia in severe cases.^{32,36,37,40-42,69,75,79} Noninvasive monitoring has been successfully used in PPCM.⁹⁵

Postoperative management

All PPCM patients should be managed in an ICU as they are prone to develop LVF and pulmonary edema in this period, requiring strict intake/output management.^{36,37,39,40,69,75} They may require vasoactive drugs, mechanical ventilation and circulatory support at any time.^{37,39-41,69,75,79} There is also high risk of thromboembolism, demanding proper anticoagulation.³⁷ Postoperative pain can be managed by RA or parenteral opioid-based techniques.^{32,37,40,42,79}

Indications for hospital admission

Milder cases can be managed at home, but moderate to severe cases will require hospital admission in the following situations:

1. Patients with LVEF less than 35% (because of high risk of thromboembolism).⁶⁵
2. NYHA class III or more symptomatic presentation (patient may need intensive management).^{11,65}
3. Patients presenting with pulmonary edema.⁸¹
4. Thromboembolic complications (increased possibility of AMI, cerebral or pulmonary embolism with catastrophic consequences).⁶⁵
5. Malignant arrhythmias causing hemodynamic disturbances.^{65,81}
6. Patients not responding or worsening with domicile treatment with evidence of vital organ dysfunction.^{65,81}

PROGNOSIS

The reported prognosis of PPCM varies in the literature, but prognosis is currently encouraging with advanced management.

Recovery from PPCM

Clinical recovery consists of improvements of symptoms and discontinuation of antifailure medications.⁴⁵ Recovery of ventricular dysfunction has been defined as (1) LVEF \geq 50% or $>$ 20% improvement and (2) LVFS \geq 30% in PPCM patients.^{19,35,44} Prognosis is related to left ventricular dysfunction at presentation.^{2,9,11} Though recovery mostly occurs in the first 2 months, it can take 6 - 12 months.^{1,2,19,35} Ninety-one percent of patients who present with LVEF $>$ 30% now recover in comparison to earlier rates of 50%.^{29,27,35,38,43,54} Complete echocardiographic normalization of cardiomegaly has also been reported.^{6,17,35,41,47} A 5-year survival rate of 94% of patients with complete recovery of ventricular function has been reported.¹³

Poor prognosis criteria

Generally patients with higher age and parity, multiple gestations, Black race, later onset ($>$ 2 weeks) of symptoms after delivery, intracardiac thrombi, cardiac conduction defects, persistence of ventricular dysfunction six months after delivery, coexisting medical illness and delay in

initiation of medical management have worse prognosis.^{1-3,5,14,27,34,35,38,54} Elderly women (≥ 35 years) have a 2.8 times greater risk of death. 28 African-Americans experience 6.4 times increased mortality compared to whites.²⁸ Higher LVEDD (> 5.6 cm), PAP and PCWP and reduced LVFS and LVSWI are usually associated with poor prognosis.^{9,14,17,19,35,38,45,54} Among these, LVEDD has been reported to be the most important prognostic indicator.^{8,35,45} The combination of high LVEDD and a left ventricular thrombus is associated with the worst prognosis.³⁵ LVEF ($< 45\%$) at two months after diagnosis has also been found to have poor prognosis.³⁵ Recently, higher dilutions of anti-Chlamydial antibody, high TNF α and IgG class 3 levels have been associated with poor prognosis.^{31,63,71} Compared to postpartum, antepartum occurrence of PPCM is associated with poor prognosis in the offspring.^{14,46}

Mortality

Mortality rates of up to roughly 50% have been reported in the literature.^{1-5,9,11,17,23-29,45,54} Approximately half die within the first month of presentation and the majority within the first three months of postpartum period.^{2,19,22,23} However late deaths occurring up to eight years later, even in the absence of subsequent pregnancy, have also been reported.^{1,14,24} The highest cause of mortality is thromboembolism, as well as severe congestive heart failure and arrhythmias.^{1,2,9,14,19,22,26,65,76} In the USA, pregnancy-related death due to cardiomyopathy has increased from 3% in the 1980s to 7.7% in the 1990s.²⁸ Among all cardiomyopathy-related deaths in 1991 - 97, 70% were attributed to PPCM.²⁸ A maternal death rate of 47.1 per 100,000 births over 5 years has been reported from Haiti, compared to that of 0.62 per 100,000 births in the USA.¹⁹ However, most patients in that Haitian study did not receive modern heart failure management. Recently, very low to even zero mortality has been reported.^{13,17,27,29,34,35,44,54} Better knowledge of pathophysiology, a multimodal approach and invasive and intensive management strategies are the cornerstones behind the recent decrease in mortality.

RISK OF RECURRENCE IN SUBSEQUENT PREGNANCY

Most reports describe recurrence of PPCM in subsequent pregnancies.^{1-4,9,14,16,21,24,34,44} It is not clear whether this is due to exacerbation of previous subclinical failures or reactivation of the same disease process.¹⁴ The highest risk of recurrence remains in patients with persistent cardiac dysfunction and the lowest risk is in those whose cardiac functions have been normalized, as evidenced by dobutamine stress test.^{1-3,9,13,21-23,43,44,47,54,76} Multiparity increases the risk of irreversible cardiac damage in subsequent pregnancies.^{11,21,23,31,65} Recurrence of heart failure ranges between 21-80% in subsequent pregnancies.^{2,3,24,34,43,44} Recently, a lower recurrence rate was reported with normalization of cardiac function.^{13,22,43,47,54} Elkayam et al. report a more than 20% reduction of LVEF in subsequent pregnancies in PPCM patients with prior normalization of cardiac function.⁴⁴ Lampert et al. found that ventricular contractile function is severely impaired in dobutamine challenge tests in apparently recovered PPCM patients.⁷⁶ Recurrence of PPCM has also been reported in patients whose ventricular size and function have returned to normal.^{2,21,43,99} Even normalization of cardiac dysfunction does not mean full correction of PPCM. There usually remains some sort of residual limitation or ECG abnormalities.^{1,2} Consequently, the present criteria used to detect the recovery of ventricular function based on resting echocardiography in PPCM patients should be revised, and the dobutamine stress test may play a vital role.^{14,43,76}

AREAS OF FUTURE RESEARCH

There has been wide variation in the incidence of PPCM worldwide. The actual incidence needs to be estimated with modified diagnostic criteria, especially in areas with extremely high incidence. Older risk factors also need to be reconsidered in this updated context. Research should be targeted towards finding the actual etiopathology, with greater emphasis on inflammatory, viral and autoimmune causes. The role of EMB in early resistant cases should be evaluated in large trials

with the help of contrast-enhanced MRI. The etiologic and diagnostic utility of autoantibodies and inflammatory cytokines should be studied. TNF α has been recommended as a target for future therapeutic options.⁵⁷ Therapeutic roles of immunoglobulin, pentoxifylline, nesiritide and levosimendan should be evaluated by larger controlled trials. Improvement of ventricular function and survival has been reported in mice with reduction in myocardial apoptosis by caspase inhibition.⁵² Caspase inhibition should be evaluated in PPCM, as myocardial apoptosis may lead to cardiomyopathy. The current prognosis of PPCM should be reassessed in the context of modern management. The role of stress echocardiography in follow up of PPCM patients with apparent normalization of cardiac function should be judged by large controlled trials.

CONCLUSION

PPCM is a rare but devastating cardiac failure of indeterminate etiology occurring in late pregnancy or early puerperium. Diagnosis of PPCM should include echocardiographic evidence of left ventricular dysfunction. Older risk and etiological factors need current reevaluation in view of modified diagnostic criteria. The present diagnostic role of EMB in PPCM is dubious but may be considered in resistant cases. Routine medical management should be started with digoxin, diuretics, vasodilators, β blockers and anticoagulants. In resistant cases, treatment with immunosuppressive drugs, immunoglobulin and pentoxifylline can be considered. Severe cases may need intensive management, including mechanical circulatory support and heart transplant. Induction of labor should be done in an intensive care setting. Cesarean section should be reserved for obstetric indications. Regional techniques are safer for labor analgesia as well as anesthesia. Invasive monitoring is recommended in severe cases. Prognosis is related to recovery of ventricular dysfunction. Future pregnancy is better avoided in patients with persistent cardiac failure. If unavoidable, subsequent pregnancy in patients with improved cardiac function should be managed in a multidisciplinary unit.

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