Peripartum cardiomyopathy (PPCM), or heart failure in association with pregnancy, was noted as early as the 1800s, but was first attributed to cardiomyopathy by Gouley and colleagues in 1937. The incidence has been reported to vary by geographic location, with rates ranging from approximately 1:15,000 pregnancies in the United States to as frequent as 1:299 in a well-studied population in Haiti and 1:100 in a small region of sub-Saharan Africa. Risk factors include hypertension, preeclampsia, multiparity, multiple gestations, African descent, and older maternal age. The prevalence of different risk factors in diverse populations may account for some of the wide range of reported prevalence estimates. Although rare, cardiomyopathy in pregnancy accounts for a significant proportion of maternal deaths, and in the United States may be increasing in frequency. Reported mortalities have ranged as high as 18% to 56%. Even when the mother survives, she may not recover myocardial function and may require chronic therapy for heart failure or cardiac transplantation. Until recently, the cause has been poorly understood. Multiple mechanisms have been postulated as the inciting cause, including inflammation, myocarditis, autoimmune reactions, apoptosis, and oxidative stress. This review addresses pathogenesis, risk factors, diagnosis, management, and prognosis.

CAUSE OF PROPOSED PATHOGENIC MECHANISMS

The investigation of the pathophysiology has been limited by the rare incidence of the disease, and the exact cause is unknown. It was previously believed that PPCM was
a result of an idiopathic dilated cardiomyopathy (IDCM) that was expressed in young, peripartal women, with a clinical and pathologic picture similar to that observed in older women or men. For many years it was believed that PPCM was a variant of IDCM that was unmasked by the hemodynamic stress of pregnancy. If this were the case, then one would expect the incidence of PPCM to be the highest during the period when greatest hemodynamic stress is achieved, which is during the second trimester. However, PPCM usually occurs in the third trimester, and even more commonly in the puerperium. Moreover, 30% of patients with PPCM experience complete recovery, with partial recovery in most cases, in contrast to rare recovery in IDCM. Moreover, PPCM is diagnosed in young women during the peripartum period, whereas IDCM is more common in the older population.

PPCM is likely its own distinct entity, and several hypotheses have been proposed regarding the pathophysiology, including viral myocarditis, abnormal immune response to pregnancy, increased myocyte apoptosis, stress-activated cytokines, maladaptive response to the hemodynamic stresses of pregnancy, excessive prolactin production, malnutrition, genetics, abnormal hormonal function, increased adrenergic tone, and myocardial ischemia (Fig. 1). Several of these etiologic mechanisms seem plausible, but none is definite.

**VIRAL MYOCARDITIS**

Pregnancy results in an immunocompromised state. The relationship between viral myocarditis and pregnancy was established as early as 1968 by Farber and Glasgow, who showed that pregnant mice were more susceptible to viral infections than nonpregnant mice. They also found that viruses multiply to a greater level in

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**Summary of Proposed Pathogenic Mechanisms for PPCM**

![Diagram of proposed pathogenic mechanisms for PPCM](image_url)

**Fig. 1. Summary of proposed pathogenic mechanisms for PPCM. (Adapted from Ntusi NB, Mayosi BM. Etiology and risk factors of peripartum cardiomyopathy: a systematic review. Int J Cardiol 2009;131:168–79; with permission.)**
the hearts of pregnant mice. The hemodynamic and physiologic changes of pregnancy may result in an increased susceptibility to viral myocarditis, higher viral loads (eg, Coxsackie and echoviruses), and worsening of myocardial viral lesions.\textsuperscript{13,14}

PPCM secondary to myocarditis in humans was first shown by Gouley and colleagues,\textsuperscript{1} who linked infection with enlarged hearts containing focal areas of necrosis and fibrosis in women dying of heart failure in the puerperium. Myocarditis has also been detected in endomyocardial biopsies in women with PPCM; however, there was a wide prevalence range among these studies (8.8%–76%).\textsuperscript{15–20} Insufficient sample sizes prohibited achieving statistical significance in any of these studies. Multiple reasons have been suggested for this variability in prevalence, including challenge in defining PPCM clinically, inclusion of patients outside the accepted time frame, timing of biopsy in relation to the onset of symptoms, variability in inclusion of patients with borderline myocarditis along with those with clear histologic myocarditis as defined by the Dallas histologic criteria, and geographic variability of affected populations.\textsuperscript{10}

Molecular studies within a German cohort of patients with PPCM found a high prevalence of virus-associated inflammatory changes and interstitial inflammation.\textsuperscript{21} It is possible that there is a postviral immune response that is directed inappropriately toward the myocardium, resulting in decreased ventricular systolic function in the setting of increased circulating volume that is characteristic of pregnancy.\textsuperscript{10} Further studies are needed to confirm the relationship between viral genomic particles and PPCM. In the future, newer technologies such as the polymerase chain reaction may be helpful in detecting viruses in the myocardium of PPCM patients.\textsuperscript{11}

### AUTOIMMUNE MECHANISMS

PPCM may be secondary to abnormal immunologic activity and inflammatory cytokines. Autoantibodies against select cardiac tissue proteins (eg, adenine nucleotide translocator, branched chain $\alpha$-keto acid dehydrogenase) have been found in women with PPCM along with increased levels of inflammatory markers (eg, tumor necrosis factor-$\alpha$, interleukin-6 [IL-6], and soluble Fas receptors).\textsuperscript{22,23} These increased markers were significantly correlated with increased left ventricular (LV) dimensions and lower LV ejection fraction in patients who presented with PPCM.\textsuperscript{23,24}

Other studies have suggested that PPCM is an acute, organ-specific, facultative autoimmune disease that is diagnosed in settings of altered immune and genetic environments.\textsuperscript{25,26} In this setting, hematopoietic fetal cells may be introduced into maternal circulation during pregnancy without being rejected as a result of the immunosuppressive state of pregnancy. These cells are attracted to cardiac tissue and are later recognized as nonself during the postpartum immune recovery, resulting in a pathologic autoimmune response.\textsuperscript{10} Antibodies have also been suggested to form against proteins from the rapidly involuting uterus (eg, actin, myosin), which may cross-react with similar proteins found in the myocardium, resulting in PPCM.\textsuperscript{10}

Warraich and colleagues\textsuperscript{27} evaluated the effect of PPCM on humoral immunity and evaluated immunoglobulins (Ig; class G and subclasses G1, G2, G3) against cardiac myosin in 47 patients with PPCM from different global regions. Compared with healthy mothers and patients with IDCm, class G and all subclass Ig were nonselectively increased in PPCM, whereas there was a selective upregulation of IgG3s in IDCm.\textsuperscript{27} Raised levels of G3-Ig in patients with chronic heart failure were found to correlate with poor clinical course at 6 month follow-up after conventional therapy.\textsuperscript{28}

These multiple studies do not show with certainty that abnormal maternal autoimmune mechanisms account for the causation of PPCM. Moreover, it is not clear
whether the autoantibodies may be secondary epiphenomena or whether they contribute directly to myocyte injury.11

CYTOKINE-MEDIATED INFLAMMATION

Investigations in molecular biology have shown that cytokines may contribute to the basic pathophysiology of cardiac failure.29 Increased levels of cytokines have also been found in the serum of women with PPCM.23 Cytokines are signaling molecules that are used extensively in cellular interaction. They are involved in a variety of biological processes, and their effects on the cardiovascular system include promotion of inflammation, intravascular coagulation, oxidative stress, cardiac structural and functional abnormalities, endothelial injury, and cardiomyocyte apoptosis.30 The proinflammatory cytokines include TNF-\(\alpha\), IL-1, IL-6, IFN-\(\gamma\), which are involved in cardiac tissue repairs that result in immediate and delayed negative inotropic effects on myocardial contractility.29,30 The inflammatory marker C-reactive protein (CRP) has been coexpressed with TNF-\(\alpha\) in the myocardium of PPCM patients, as well as other human cardiomyopathies.31 It is believed that in PPCM, as in other conditions that result in heart failure, the LV end-diastolic wall stress results in myocardial expression of a proinflammatory cytokine network, which influences cardiac contractile performance and promotes maladaptive ventricular remodeling, leading to heart failure.29

HEMODYNAMIC STRESS OF PREGNANCY

The cardiovascular changes in pregnancy are characterized by a high-volume, low-resistance state, with cardiac output increased up to 30% or 40% by the second and third trimester. These changes normally persist up to 2 or 3 weeks post partum, and may not resolve to normal physiology until 12 weeks post partum. It is believed that PPCM may be due to an exaggerated decrease in systolic function in the presence of the marked hemodynamic changes of pregnancy.

Echocardiographic and Doppler analysis of cardiac hemodynamics in normal pregnancy showed a 10% increase in preload (LV end-diastolic volume), a 45% increase in cardiac output, and a 28% decrease in afterload (end-systolic wall stress), with LV remodeling and transient LV hypertrophy.32,33 Although LV anatomy may return to normal after pregnancy, contractile reserve in patients with PPCM was found to be decreased when assessed by dobutamine stress echocardiography.34 There are not enough convincing data currently to support this hypothesis as the underlying cause for PPCM.

INCREASED MYOCYTE APOPTOSIS

Various animal models of heart failure have shown terminally differentiated cardiac myocytes undergoing apoptosis, or programmed cell death, as the final common pathway in cardiac disorders such as dilated and ischemic cardiomyopathy and acute myocardial infarction (MI).35,36 It is believed that disruption of this homeostatic mechanism may lead to uncontrolled cellular proliferation and excessive cell death.37 Studies have reported the G protein Gq to be responsible for coupling several cell surface receptors to intracellular signaling pathways involved in cardiac myocyte hypertrophy and cardiomyocyte apoptosis.38,39 Apoptosis, which is mediated by proteases termed caspases, can be reduced by caspase inhibitors, which have been shown to improve LV function and survival in pregnant G\(\alpha\)q mice.40 However, controversy still exists on the relevance of apoptosis to the development of PPCM.
EXCESSIVE PROLACTIN PRODUCTION

The involvement of prolactin in PPCM has been suggested, but recent studies have confirmed the potential role of excessive prolactin production in the pathogenesis of PPCM in mice and women. Increased blood volume, decreased blood pressure, decreased angiotensin responsiveness, increased erythropoietin levels, reduced renal excretion of water, sodium, and potassium are all associated with prolactin. A high incidence of PPCM has been noted in knockout mice for STAT-3, a cardiac tissue-specific DNA-binding protein. STAT-3 is involved in mediating cardiomyocyte hypertrophy and myocardial angiogenesis but also protects the heart from oxidative stress by upregulating antioxidative enzymes (eg, manganese superoxide dismutase [MnSOD]). Reduced levels of STAT-3 lead to increased oxidative stress and activation of cathepsin D, resulting in cleavage of prolactin into an antiangiogenic and proapoptotic 16-kDa isoform. Treatment of STAT-3–deficient pregnant mice with bromocriptine, an inhibitor of prolactin secretion, prevents the development of PPCM in these mice.

NUTRITION

Nutrition was believed to play a role in the pathogenesis of PPCM. For example, selenium deficiency, which increases cardiovascular susceptibility to viral infection, hypertension and hypocalcemia, was detected in women with PPCM from the Sahel region of Africa. Excessive salt consumption, leading to volume overload, may also be linked to PPCM. However, malnutrition likely does not play a role in the cause of PPCM because many occurrences of the disease are documented in well-nourished patients.

GENETICS

Some case reports suggest a possible familial clustering of PPCM. In each of these instances of women diagnosed with PPCM, at least 1 first-degree relative had also experienced PPCM. There are also animal studies that suggest a genetic susceptibility to viral myocarditis in animals deficient in transforming growth factor-β (TGF-β); however, more studies are needed to investigate the role of TGF-β in PPCM.

OTHER CAUSES

Abnormal hormonal regulation has been proposed as a potential cause of PPCM. The heart undergoes homeostatically regulated remodeling during pregnancy, including hypertrophy and growth of the capillary network to accommodate the increased pregnancy-related hemodynamic volume load and to maintain normal maternal-fetal health. Estrogen is believed to promote cardioprotection during pregnancy, and the sudden drop noted after delivery of the placenta might explain why gravidas experience heart failure after delivery. Relaxin, another ovarian hormone produced during pregnancy that promotes excessive relaxation of the cardiac muscle, may also play a role in PPCM. There is a lack of convincing evidence that abnormal hormone levels result in PPCM.

Increased adrenergic tone secondary to emotional or physical stress has been implicated in the pathogenesis of PPCM, resulting in fluid overload, reduced colloid osmotic pressure, and transient LV dysfunction. β1-adrenergic receptor antibodies may also play a role in PPCM, and, together with increased adrenergic tone, may contribute to cardiac muscle dysfunction.
Vascular disease as a possible cause of PPCM has also been suggested, but coronary arteries were found to be normal when coronary angiography was performed.64,65 Pathologic specimens also negate the possibility of vasculitis or intermittent coronary spasms.66

**RISK FACTORS**

Several risk factors are believed to be associated with the development of PPCM, including prolonged tocolysis, advanced maternal age, high gravidity/parity, multipregnancy, race, socioeconomic status, gestational hypertension, and cocaine abuse.11 The use of prolonged tocolytics, such as terbutaline, ritodrine, salbutamol, isoxsuprine, and magnesium sulfate, has been known to cause pulmonary edema but has also been associated with LV dysfunction in the peripartum period.67,68 The physiologic side effects of these drugs via interaction with β receptors include tachycardia, hyperglycemia, hypokalemia, and water retention. Cardiac failure and tocolysis seem to be unique in pregnancy, as these same medications, used for various other conditions, do not result in similar complications in nonpregnant women.11 The underlying mechanisms by which these drugs might cause heart failure in pregnancy include (1) increased circulating blood volume resulting in overload; (2) prolonged β-sympathomimetic stimulation resulting in prolonged tachycardia as well as decreased serum albumin concentration and colloid oncotic pressure; (3) increased aldosterone and antidiuretic hormone secretion resulting in decreased excretion of sodium and water.11,69

Advanced maternal age was believed to be a risk factor for PPCM. In a review of several case series of patients with PPCM, their mean age was approximately 30 years.9,23,70,71 However, the prevalence in all of the aforementioned studies was greatest in women at the upper and lower extremes of child-bearing age.11 In terms of gravidity/parity as risk factors, PPCM has been documented to occur more often in women with high gravidity and parity.9,23,71 Moreover, although most women with PPCM have a singleton pregnancy, the prevalence among women with multiple gestations is much higher.72

PPCM has been reported among a variety of races, including people of Caucasian, Hispanic, Asian, and African descent.9,71,73 However, PPCM is generally believed to be more prevalent in women of African descent,11 although it is not clear whether race is an independent risk factor or an association. Moreover, pregnancy-related hypertension and preeclampsia are also known risk factors for PPCM. However, some have debated whether to exclude pregnancy-related hypertensive disorders from the diagnosis of PPCM, although most investigators believe them to be separate entities. LV recovery at 6 months may be more frequent among women who suffered preeclampsia in contrast to those without this history.11

**DIAGNOSIS**

A thorough history and physical examination should be performed to identify cardiac and noncardiac disorders that may contribute to development or exacerbation of heart failure in pregnancy. This requirement includes attention to the presence of hypertension (chronic, gestational, preeclampsia), diabetes, dislipidemia, coronary, rheumatic or valvular heart disease, prior chemotherapy or mediastinal radiation, sleep disorders, current or past alcohol or drug use, collagen vascular disease, sexually transmitted diseases, thyroid disease, arrhythmias, and family history of cardiomyopathy or sudden death. Current use of alcohol, tobacco, illicit drugs or alternative therapy, diet, and sodium intake should also be assessed. Assessment should be made of
the patient’s ability to perform activities of daily living. Careful evaluation of volume status should be performed, including orthostatic blood pressure changes, weight, height, and body mass index. Initial laboratory assessment should include complete blood count, urinalysis, serum electrolytes including calcium and magnesium, fasting glucose and hemoglobin A1C, lipid profile, liver function tests, and thyroid-stimulating hormone. Measurement of natriuretic peptides (brain natriuretic peptide [BNP] and N-terminal pro-BNP [NT pro-BNP]) can be helpful in assessment of volume status and risk stratification, although criteria for abnormalities need to be adjusted in pregnancy. Increased BNP levels have been associated with reduced ejection fraction, LV hypertrophy, increased LV filling pressures, acute MI/ischemia, and preeclampsia, although they can occur in other settings such as pulmonary embolism or chronic obstructive pulmonary disease and may not be increased in the setting of morbid obesity.74–78

Twelve-lead electrocardiogram and posterior-anterior and lateral chest radiograph should be part of the initial assessment of all patients with clinical heart failure. Two-dimensional echocardiography with Doppler should also be performed to assess LV size, wall thickness, and valvular function, and can give clues to the presence of other precipitating causes such as rheumatic or congenital heart disease. Magnetic resonance imaging (MRI) may play an important role in the diagnosis of PPCM and assist in identifying the mechanism involved.79 MRI can provide assessment of morphology and function, and has the ability to display myocardial fibrosis as a consequence of myocarditis through delayed contrast enhancement technique.80 Radionuclide ventriculography or coronary arteriography in the nonpregnant patient may be considered for patients with symptoms or history suggestive of angina or underlying coronary disease without contraindication to revascularization. Noninvasive testing for myocardial ischemia may be substituted for some patients in this setting.

Additional screening for hemochromatosis, sleep disorders, human immunodeficiency virus (HIV), rheumatologic disease, amyloidosis, or pheochromocytoma should be based on clinical suspicion. Endomyocardial biopsy should not be performed routinely, although it is occasionally useful if there is suspected giant cell myocarditis as in autoimmune disorders, thymoma, drug hypersensitivity, anthracycline therapy, restrictive cardiomyopathy, sarcoid, or suspected arrhythmogenic right ventricular dysplasia.81

The diagnosis of PPCM is a diagnosis of exclusion (Box 1), but should be suspected whenever women present with symptoms of heart failure during the peripartum period. The diagnosis may be challenging because symptoms such as dizziness,

**Box 1**
**Clinical criteria for the diagnosis of PPCM**

- Development of cardiac failure in the last month of pregnancy or within 5 months postpartum
- Absence of another identifiable cause for the cardiac failure
- Absence of recognizable heart disease before the last month of pregnancy
- LV systolic dysfunction shown by echocardiographic data such as depressed shortening fraction (eg, ejection fraction less than 45%, M-mode fractional shortening less than 30%, or both, and an LV end-diastolic dimension of more than 2.7 cm/m²)

dyspnea, fatigue, or pedal edema of normal late pregnancy are similar to symptoms of early congestive heart failure.\textsuperscript{82} Some would argue that the criteria for diagnosis in the last month of pregnancy are outdated and should be revised to include the entire span of pregnancy.\textsuperscript{71,83}

There are currently no specific clinical criteria for differentiating between symptoms of normal late pregnancy and heart failure. One should have a high index of suspicion in any woman experiencing paroxysmal nocturnal dyspnea, chest pain, nocturnal cough, new regurgitant murmurs, pulmonary crackles, increased jugular venous pressure, or hepatomegaly.\textsuperscript{82} Determining the presence of LV dysfunction is critical to the diagnosis.\textsuperscript{84}

**MANAGEMENT OF HEART FAILURE**

Therapy is directed to improving symptoms, slowing progression of LV dysfunction, and improving survival, as summarized in Box 2.

Nonpharmacologic therapy, including fluid restriction and low-sodium diet for patients with evidence of volume overload, monitoring for pedal edema and measurement of daily weight are useful adjuncts. Control of blood pressure is a key component of therapy. Current guidelines for management of chronic heart failure include combinations of 3 types of drugs: diuretics, angiotensin-converting enzyme inhibitors

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**Box 2**

**Recommended therapy for PPCM**

- **Goals**
  - Treat hypertension
  - Fluid restriction
  - Dietary salt restriction
  - Routine exercise post partum if stable
- **Drugs for routine use**
  - Diuretics
  - \(\beta\)-Blockers
  - Vasodilators
  - Digoxin\textsuperscript{a}
- **Therapies in selected patients**
  - Aldosterone antagonists
  - Inotropes
  - Anticoagulation
  - Implantable defibrillators
  - Biventricular pacing
  - Cardiac transplantation

\textsuperscript{a} See text for details.

(ACEIs) or angiotensin receptor blockers (ARBs), and β-blockers. In women with PPCM, these recommendations need to be modified based on current gravid status and the woman’s desire to lactate. Commonly used therapeutic agents with indications and precautions are summarized in Table 1. Management of PPCM should be performed in conjunction with a cardiologist versant in the use of these drugs in pregnancy.

Diuretics are indicated for most patients because they can improve pulmonary and peripheral edema within hours or days, but are usually inadequate to maintain clinical volume status in the absence of additional therapy. Furosemide, a loop diuretic, is most commonly used, but thiazides may be added if the loop diuretics are insufficient. Adverse effects are noted in Table 1. We typically use diuretics in the gravida with clear evidence of volume overload as well as early after delivery when volume shifts can be expected to increase intravascular volume. Aldosterone antagonists have been shown to improve survival in selected heart failure patients; these agents can be added post partum but we have not currently used these in pregnancy.

ACEIs improve survival in all severities of myocardial disease, but have multiple teratogenic risks and are typically avoided in pregnancy. When initiated post partum, we suggest that the patient should be counseled about the potential for teratogenicity or fetal demise with a recurrent pregnancy and appropriate steps for birth control be implemented. The risk/benefit ratio should be weighed for use in lactating mothers, although we have often prescribed these agents in this setting. For patients who are candidates for ACEIs, therapy is initiated at low dosages and titrated at intervals to a maximal tolerated dose.

ARBs are recommended because they improve mortality in patients with current or prior heart failure who do not tolerate ACEIs; it is not clear whether adding ARBs to ACEIs is beneficial. Teratogenic risks of ARBs are similar to those with ACEIs and we use similar precautions and counseling.

Hydralazine is an arterial vasodilator with little effect on venous tone and filling pressures. A large clinical experience with hydralazine in treating hypertension in pregnancy suggests that it is safe, and it is compatible with breast feeding. Nitrates decrease dyspnea and improve exercise tolerance. We currently use hydralazine and nitrates as the vasodilators of choice for women who are pregnant or if medications acting on the renin-angiotensin system are contraindicated, but ACEIs remain the first-line agent for nonpregnant patients. The combination of hydralazine and nitrates is considered to be a reasonable addition to standard therapy in symptomatic patients and some racial groups. Amlodipine is an additional option for vasodilator therapy, especially if hydralazine is not tolerated or the patient has chronic hypertension. Goal systolic blood pressure is 100 to 110 mm Hg for most patients. We do not usually decrease doses of vasodilators for asymptomatic hypotension.

Three β-blockers (sustained-release metoprolol succinate, carvedilol, and bisoprolol), have been shown to reduce mortality with current or prior heart failure and reduced ejection fraction, and is therefore recommended for all stable patients unless contraindicated. Metoprolol is considered compatible with breast feeding, but we recommend monitoring of exposed neonates for signs and symptoms of β blockade, such as bradycardia, hypoglycemia, and growth restriction. Because transient worsening of heart failure symptoms has been reported with initiation of therapy, patients should have minimal evidence of fluid retention and not have required recent intravenous inotropic therapy. Initial therapy is started at a low dose, then doubled at 2-week intervals to achieve the target dose or until limited by symptoms. Improvement seems to be dose dependent; therefore target doses should be those noted in clinical heart failure trials.
<table>
<thead>
<tr>
<th>Medication</th>
<th>Indication</th>
<th>Drug Effect</th>
<th>Precautions</th>
<th>Maternal</th>
<th>Fetal</th>
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<tbody>
<tr>
<td>Diuretics</td>
<td>Evidence of volume overload or fluid retention</td>
<td>↓ Preload and afterload</td>
<td>Electrolyte abnormalities, fluid depletion, hypotension, azotemia</td>
<td>Decreased placental perfusion</td>
<td>Thiazides: possible ↑ risk of birth defects or fetal thrombocytopenia</td>
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<tr>
<td>Furosemide</td>
<td>(first line)</td>
<td>Improve cardiac function</td>
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<tr>
<td>Thiazides</td>
<td>(second line)</td>
<td>Decrease edema, improve exercise tolerance</td>
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<tr>
<td>ACE inhibitors</td>
<td>History of LV dysfunction, stage B and C heart failure in the nonpregnant state</td>
<td>↓ preload and afterload</td>
<td>Electrolyte abnormalities</td>
<td>Skull hypoplasia, anuria, renal failure, limb contractures, craniofacial deformation, hypoplastic lungs, death</td>
<td></td>
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<tr>
<td>Lisinopril</td>
<td></td>
<td>Improves survival in all severities of myocardial disease</td>
<td>Hypotension</td>
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<td>Enalapril</td>
<td></td>
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<td>Cough</td>
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<td>Captopril</td>
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<td>Angioedema</td>
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<td>ARBs</td>
<td>Intolerance to ACE inhibitors</td>
<td>↓ preload and afterload</td>
<td>Similar to ACE inhibitors</td>
<td>Similar to ACE inhibitors</td>
<td></td>
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<tr>
<td>Valsartan</td>
<td></td>
<td>Improves mortality</td>
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<td>Candesartan</td>
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<tr>
<td>Peripheral vasodilators</td>
<td>First-line vasodilator in pregnancy as ACE and ARBs are contraindicated</td>
<td>↓ preload and afterload</td>
<td>Hypotension</td>
<td>Tolerance with long-term nitrate therapy</td>
<td></td>
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<tr>
<td>Hydralazine</td>
<td></td>
<td></td>
<td>Headache with nitrates</td>
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<td>Nitrates</td>
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<td>Lupuslike reaction with hydralazine</td>
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<td>Nesiritide</td>
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<tr>
<td>Calcium channel blocker&lt;sup&gt;C&lt;/sup&gt;</td>
<td>Blood pressure control</td>
<td>Peripheral vasodilation</td>
<td>Peripheral edema</td>
<td>Hypotension</td>
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<tr>
<td><strong>Amlodipine</strong>&lt;sup&gt;L3&lt;/sup&gt;</td>
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<td><strong>β-Blockers</strong>&lt;sup&gt;C&lt;/sup&gt;</td>
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<tr>
<td>Metoprolol&lt;sup&gt;L3&lt;/sup&gt;</td>
<td>Always used with LV dysfunction unless contraindicated</td>
<td>Improves myocardial contractility by ↓ sympathetic tone</td>
<td>Transient worsening of congestive heart failure symptoms</td>
<td>Bradycardia, hypoglycemia, growth retardation</td>
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<tr>
<td>Carvedilol&lt;sup&gt;L3&lt;/sup&gt;</td>
<td></td>
<td>Reduces mortality</td>
<td></td>
<td>Animal fetal and teratogenicity with carvedilol at high human dose</td>
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<tr>
<td>Bisoprolol&lt;sup&gt;L3&lt;/sup&gt;</td>
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<th><strong>Inotropes</strong></th>
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<tr>
<td>Digoxin&lt;sup&gt;C,L2&lt;/sup&gt;</td>
<td>Symptomatic heart failure in pregnancy</td>
<td>↑ myocontractility</td>
<td>Arrhythmias gastrointestinal symptoms</td>
<td></td>
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<tr>
<td>Dopamine&lt;sup&gt;C,L2,b&lt;/sup&gt;</td>
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<td>Dobutamine&lt;sup&gt;B,L2,b&lt;/sup&gt;</td>
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<th><strong>Aldosterone antagonists</strong></th>
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<tr>
<td>Spironolactone&lt;sup&gt;C-D,L2&lt;/sup&gt;</td>
<td>May add post partum to ACEI and Arb in symptomatic patients</td>
<td>Improves survival in patients with class 3–4 symptoms</td>
<td>Hyperkalemia</td>
<td>Feminization of male rat fetuses</td>
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<tr>
<td>Eplerenone&lt;sup&gt;B,L3&lt;/sup&gt;</td>
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Dr Hale’s Lactation Risk Category: L1, controlled studies in breastfeeding women fail to show a risk to the infant and the possibility of harm to the breastfeeding infant is remote, or the product is not orally bioavailable in an infant; L2, drug that has been studied in a limited number of breastfeeding women without an increase in adverse effects in the infant. Or, the evidence of a demonstrated risk that is likely to follow is remote; L3, there are no controlled studies in breastfeeding women, but the risk of untoward effects to a breastfed infant is possible. Or, controlled studies show only minimal nontreating adverse effects. Give if potential benefits outweigh risks. Drugs in this category are essentially compatible with breastfeeding. (Data from Hale TW. Medications and mother’s milk. 12th edition. Amarillo, TX: Hale Publishing; 2006.)

<sup>a</sup> Denotes US Food and Drug Administration class (A, B, C, D) and lactation safety.
<sup>b</sup> Reserved for refractory heart failure.
Digoxin improves symptoms, quality of life, and exercise tolerance in mild-to-moderate heart failure by attenuation of the neurohormonal system and inhibition of sodium potassium adenosine triphosphatase leading to increased myocontractility. Benefit with digoxin therapy has been shown regardless of underlying rhythm, cause of heart failure, or nature of concomitant therapy, but does not decrease mortality in class 2 or 3 heart failure. Digoxin has a narrow therapeutic index and there have been concerns about increased morbidity and mortality when this agent is used; therefore attention is required to avoid toxicity. We usually keep serum levels to between 1 and 1.2 ng/dL or less. However, we typically add digoxin early in the course of therapy in symptomatic women when ACEIs and ARBs are contraindicated.

For patients with ejection fraction of 35% or less on optimal therapy who have an expected survival of more than 1 year, implantable cardioverter defibrillator therapy may be warranted for primary prevention of sudden cardiac death. Cardiac resynchronization therapy is recommended in patients with widened quantitative radiosintigraphy (QRS) by electrocardiograph (ECG) and class 3 or 4 symptoms despite optimal medical therapy. LV-assist devices and transplantation are therapeutic options in the most critical patients.

LV dysfunction is associated with an increased risk of thromboembolic phenomena. In 3 large contemporary heart failure trials risk of embolic events ranged from 1 to 2.5 per 100 patient years. Risk of embolic event correlated with severity of heart failure, presence of atrial fibrillation, and thrombus noted on transthoracic echocardiography. Furthermore, pregnancy and the puerperium are prothrombotic states. A recent review of 182 patients with PPCM documented thromboembolic complications in 4 patients (2.2%). Choosing a specific antithrombotic agent during pregnancy is complicated by potential for teratogenicity with warfarin and dosing issues with heparin. In their practice, during pregnancy when warfarin is contraindicated, we have used low-molecular heparin in therapeutic doses when ejection fraction is 30% or less, atrial fibrillation is present, or there is documented thrombus/prior cardiac embolic event. Therapeutic dosing is typically based on weight to achieve an anti-Xa level of 0.6 to 1 IU/mL (enoxaparin) or 0.85 to 1.05 IU/mL (dalteparin). Warfarin can be used post partum in this setting to achieve an international normaliza-

 Drugs known to adversely affect clinical status in heart failure should be avoided whenever possible, including nonsteroidal antiinflammatories, many antiarrhythmic drugs, and nondihydropyridine calcium channel blockers. Exercise training can be an adjunct to improving status in stable post partum patients.

Acute heart failure decompensation is usually manifested by signs of worsening pulmonary or peripheral congestion, particularly dyspnea, tachycardia, decreased oxygen saturation, large weight gain, and signs and symptoms of hypoperfusion such as hypotension or worsening mental status. The normal hemodynamic changes of pregnancy can make recognition of this syndrome difficult, but the presence of basilar rales, jugular venous distension, positive abdominal jugular reflex, increased heart rate, S3, and peripheral edema (all findings that can be normal in pregnancy) should raise the index of suspicion, particularly in those with a previous history of heart failure. Measurement of natriuretic peptides (BNP, NT pro-BNP) can be useful adjuncts to diagnosis.

A search should be made for potentially confounding factors such as acute lung injury, embolus, pneumonia, preeclampsia, or MI. Therapy is directed at treatment of volume overload, afterload reduction, hypertension control, and treatment of confounding factors such as arrhythmias, anemia, and thyroid disease.
Oxygen therapy should be administered to relieve symptoms related to hypoxemia. With significant volume overload we typically initiate loop diuretic therapy with furosemide, although caution must be used in the presence of preeclampsia because of concern for decreased placental perfusion. In pregnancy, hydralazine and nitrates are the vasodilators of choice because ACEIs and ARBs are contraindicated. Although evidence that digoxin is beneficial in acute decompensated heart failure is lacking, we have usually empirically added this drug. We use the same approach to β blockade in pregnant women as in nonpregnant women: initiation of β blockade once volume status has improved; in women already on this therapy it can often be continued, although occasionally dosage needs to be diminished. Intravenous nitroglycerine may be required in more severely decompensated patients, and inotropic therapy with dobutamine may be necessary in the setting of hypoperfusion with clearly increased filling pressures. Few human data are available, but, if blood pressure support is required, dopamine may have fewer potentially deleterious effects on placental blood flow than phenylephrine or norepinephrine. Intravenous nitroprusside or nesiritide may be considered in certain circumstances for afterload reduction, although thiocyanate toxicity must be considered with the former and there are few human data in pregnancy with the latter. Invasive monitoring may be considered for patients with respiratory distress or impaired perfusion in which intracardiac filling pressures cannot be determined from clinical assessment.

OTHER NOVEL THERAPIES

In mouse models of PPCM, increased activity of cardiac cathepsin D promotes activity of a 16-kD proapoptotic form of prolactin, leading to myocardial injury. Bromocriptine as a specific therapy for PPCM is currently being evaluated. Several case reports documenting recovery of function in women with PPCM treated with bromocriptine have been published. A series of 12 patients with previous PPCM at high risk for redevelopment were randomized to standard therapy with or without bromocriptine. In the 6 patients treated with bromocriptine there was no recurrence, whereas all patients treated with standard therapy alone developed worsening function. MI has rarely been reported in women taking bromocriptine for suppression of lactation. Hilfiker-Kleiner noted no complications in 18 PPCM women treated consecutively with bromocriptine (Denise Hilfiker-Kleiner, MD, Johannesburg, South Africa, personal communication, December 2009). Use of bromocriptine must be weighed against potential harm of decreased milk production, especially in Third World countries where risk of infant infection and malnutrition are high. Ongoing prospective trials should clarify the decision to treat with this agent.

In a study of 59 patients with PPCM, 30 were treated with pentoxifylline, which is known to decrease TNF-α, in addition to standard therapy with digoxin, ACEIs, and β blockade. They had lower mortality, greater decrease in LV end-diastolic and systolic chamber dimensions, and greater increase in functional status than the group treated with standard therapy alone. Intravenous immune globulin has been associated with improved ejection fraction in several studies of cardiomyopathy associated with active inflammation; however, treatment effect could not be proved because of a marked variability in outcome measures and the high rate of spontaneous recovery. Immunosuppressive therapy has been considered to be helpful in some patients with active myocarditis, although active viral infection must be excluded. None of these novel agents are currently routinely recommended. A multicenter PPCM network is currently being established. Results of studies performed via this network
should fuel development of prospective investigations with adequate power to address pathogenesis and new treatments for PPCM.

ANTEPARTUM MANAGEMENT

Serial clinical assessment should be performed at each return visit to assess the patient’s ability to perform routine and desired activities of daily living, blood pressure, heart rate, weight, and volume status. Repeat assessment of ejection fraction and structural heart changes should be performed in patients who have had a change in clinical status, at intervals, and usually again before delivery. The value of serial measurements of BNP to guide therapy in pregnant patients with heart failure is not well established but in our practice we have found it a useful adjunct. Serum electrolytes and renal function should be monitored frequently. Potassium and magnesium concentrations are of particular importance because deficiency is a common adverse effect of diuretic therapy and a contributing factor to digoxin toxicity and fatal arrhythmias. Increased potassium levels are of potential concern in patients treated with ACEIs, ARBs, or aldosterone antagonists, although these are not routinely used in pregnancy.

We typically perform a sonogram at 20 weeks’ gestation to assess fetal anatomy, and then serially to assess fetal growth, particularly for intrauterine growth restriction. In the third trimester, we routinely perform antenatal testing (eg, nonstress test and amniotic fluid index or biophysical profile) starting at 32 weeks and then weekly thereafter. If steroids for fetal lung maturity are indicated preterm, this medication can be administered safely with careful attention to the potential for fluid retention.

Fett recently proposed a focused medical history test for PPCM patients during the latter portion of the pregnancy and post partum period, evaluating for orthopnea, dyspnea, unexplained cough, lower extremity swelling, excessive weight gain, and palpitations. Patients are assigned points based on symptomatology; tests for natriuretic peptide levels and high-sensitivity CRP (hs-CRP) are performed if the patient has 3 to 4 points or more, with repeat echocardiography if these are increased. Fett recommends performing all 3 tests if the patient reports symptoms resulting in 5 or more points. Prospective validation of this point scale in the future will be important in verifying risk.

MANAGEMENT OF DELIVERY

If medical management is successful in stabilizing a patient with PPCM, then early delivery is not required and spontaneous labor is not contraindicated. However, if the converse is true, then early delivery may be desirable. Labor induction can be conducted with minimal risk and, if cervical ripening is required, prostaglandins can be administered safely, as can oxytocin. One should consider administration of an early epidural to minimize sympathetic output; however, caution must be exercised in limiting fluid boluses and maintaining strict intake and output to avoid fluid overload. A predelivery anesthesia consultation is desirable in planning the anesthetic choice. Shortening the second stage of labor with the use of low forceps or a vacuum device is recommended to minimize ventricular work. Given the potential surgical risks encountered with cesarean delivery, including infection, blood loss, greater fluid shifts, and postoperative complications, we believe the cardiovascular benefits from vaginal delivery most often outweigh that of surgical delivery. We typically reserve cesarean delivery for obstetric indications; however, the need for prompt delivery may a play a role in the obstetrician’s decision. Placement of invasive catheters for monitoring (eg, Swan-Ganz) have not been proven to achieve better outcomes in perioperative.
trials. We reserve invasive monitoring for individuals in whom volume status is problematic. Thromboprophylaxis should be considered intrapartum (eg, sequential compression devices or prophylactic heparin). Strict monitoring of fluid status is critical, and we often administer diuretic therapy after delivery to prevent volume overload as fluids are resorbed into the intravascular space after delivery. The parturient should be seen 1 week after delivery to assess her cardiovascular status and make any necessary medication adjustments.

MATERNAL PROGNOSIS

Reports of long-term prognosis in women with PPCM vary, but outcome depends on LV function. Chapa and colleagues reviewed 32 PPCM patients and noted that fractional shortening of less than 20% and LV end-diastolic dimension of 6 cm or more at diagnosis were associated with a threefold greater risk for persistent LV dysfunction. Amos and colleagues reported 55 PPCM cases from 1990 to 2003, mean follow-up 43 months, and their mean initial ejection fraction was 20%. In this cohort, 62% of patients improved, 24% remained unchanged, and 4% died, whereas 10% required cardiac transplantation. Most who recovered significant LV function showed evidence of improvement by 2 months after diagnosis. Predictors of poor outcome included enlarged LV end-diastolic dimension (>5.6 cm), presence of LV thrombus, and African American race. Goland and colleagues recently reviewed 182 PPCM patients for major adverse events (MAE) defined as death or life-threatening complications including heart transplantation, temporary circulatory support, cardiopulmonary arrest, pulmonary edema requiring intensive care unit therapy, thromboembolic complications, ventricular arrhythmias leading to placement of an implantable cardioverter defibrillator or bradyarrhythmias leading to pacemaker placement. Mean age was 29 (±7) years, follow-up 19 (±25) months (range 0–168 months) and ejection fraction 29% (±11%). MAE were noted in 25% of patients and 13 (7%) died: 5 of sudden cardiac death, 6 with progressive heart failure, and 2 from unknown causes. Eleven patients underwent heart transplantation (6%), whereas severe pulmonary edema was noted in 17 (9%) and thromboembolic complications in 4 (2.2%) women. All patients with MAE had severe LV dysfunction, were more commonly non-Caucasian, and more often had a delayed diagnosis. Greater complication rates in non-Caucasian women may reflect genetic or environmental status or disparities in access to health care. Similarly, Sliwa and colleagues studied 100 women with newly diagnosed PPCM at a single center in South Africa for 6 months and noted normalization of LV function in only 23%. Fifteen patients died: 4 suddenly, the rest of progressive heart failure despite optimal medical therapy. Transplantation and placement of an LV-assist device were not available for financial reasons. Plasma markers of inflammation were significantly increased in PPCM patients, and correlated with lower ejection fraction and increased LV dimensions at presentation. Patients who died had a significantly lower mean ejection fraction and higher Fas/Apo-1 plasma levels.

Prognosis with Recurrent Pregnancies

Many women with PPCM desire another pregnancy. Information about risk of recurrent LV dysfunction is based predominantly on retrospective reviews of women who undertook subsequent pregnancies. Elkayam and colleagues reviewed the risk of recurrent cardiomyopathy from a survey of 44 patients who underwent 60 subsequent pregnancies. Subjects were divided into those whose LV function normalized before recurrent pregnancy and those in whom LV function remained diminished. During subsequent pregnancy mean ejection fraction decreased in both groups, and heart
failure symptoms were noted in 21% of gravidas with normal LV function and 44% of those with persistent dysfunction; mortality was 19% in those with persistent LV dysfunction. Prematurity was more frequent in the women with LV dysfunction. Fett and colleagues\textsuperscript{103} documented 61 women with recurrent pregnancies identified from a Haitian PPCM registry or Internet support group and noted recurrent heart failure in 29% percent. As in the analysis by Elkayam and colleagues\textsuperscript{102} LV function at the start of pregnancy predicted recurrent heart failure at a rate of 46.2% when ejection fraction was less than 55%. Risk was inversely related to ejection fraction, with recurrent cardiomyopathy documented in only 17% of those with ejection fraction greater than 55%, compared with 66.7% recurrence in women with ejection fractions less than 45%.

There are no established protocols for following women with recurrent pregnancies who elect to continue pregnancy. Exercise stress echocardiography or dobutamine stress echocardiography may help define risk in women with recovered function.\textsuperscript{34} Some patients with apparent improvement in LV function may still have decreased contractile reserve that becomes evident only with stress testing. Normal cardiac reserve does not preclude recurrent PPCM in any of the studies detailing recurrent pregnancy.\textsuperscript{83,102,103} All patients, even those with recovered function, should be considered high risk, and close communication between the treating maternal-fetal medicine expert and cardiologist, and at time of delivery the obstetric anesthesiologist and perinatologist, is mandatory. Based on clinical experience with 61 recurrent gravidas, Fett\textsuperscript{99} proposed baseline echocardiographic evaluation of LV function with follow-up evaluation in second and third trimesters, and in the first month post partum or if there is a change in symptoms suggestive of recurrent heart failure. Baseline BNP or pro-BNP and hs-CRP levels, with repeat values performed near term or with symptoms, can also provide useful clues to increased volume status suggestive of recurrent heart failure and increased inflammation associated with impending relapse, respectively. As the pathophysiology of PPCM becomes increasingly better defined, specific cytokine markers may prove useful adjuncts to predicting risk.

**SUMMARY**

Although multiple mechanisms have been postulated, PPCM continues to be a cardiomyopathy of unknown cause. Multiple risk factors exist and the clinical presentation does not allow differentiation among potential causes. Although specific diagnostic criteria exist, PPCM remains a diagnosis of exclusion. Treatment modalities are dictated by the clinical state of the patient, and prognosis is dependent on recovery of function. Randomized controlled trials of novel therapies, such as bromocriptine, are needed to establish better treatment regimens to decrease morbidity and mortality. The creation of an international registry will be an important step to better define and treat PPCM.

**REFERENCES**


