



**EDUCATIONAL OBJECTIVE:** Readers will suspect peripartum cardiomyopathy in patients who develop unexplained heart failure symptoms during the peripartum period

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# Peripartum cardiomyopathy: Causes, diagnosis, and treatment

## ABSTRACT

Peripartum cardiomyopathy is a life-threatening condition of unknown cause that occurs in previously healthy women during the peripartum period. It is characterized by left ventricular dysfunction and symptoms of heart failure that can arise in the last trimester of pregnancy or up to 5 months after delivery. We review its possible causes and how to recognize and manage it.

## KEY POINTS

Heightened suspicion is important when a pregnant woman presents with signs of heart failure, because early diagnosis allows proven treatment to be started.

Standard heart failure therapy should be started in postpartum patients with this disease, using available local protocols.

Pregnant women should not receive angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or warfarin because of potential teratogenic effects.

An initial left ventricular end-systolic dimension less than 5.5 cm, a left ventricular ejection fraction greater than 30%, and a low cardiac troponin level may predict a better outcome.

Subsequent pregnancies carry a high risk of relapse, even in women who have fully recovered left ventricular function.

**H**EART FAILURE DURING PREGNANCY WAS recognized as early as 1849, but it was first described as a distinctive form of cardiomyopathy only in the 1930s.<sup>1</sup> In 1971, Demakis et al<sup>2</sup> described 27 patients who presented during the puerperium with cardiomegaly, abnormal electrocardiographic findings, and congestive heart failure, and named the syndrome *peripartum cardiomyopathy*.

The European Society of Cardiology<sup>3</sup> recently defined peripartum cardiomyopathy as a form of dilated cardiomyopathy that presents with signs of heart failure in the last month of pregnancy or within 5 months of delivery.

Peripartum cardiomyopathy is relatively rare but can be life-threatening. The National Hospital Discharge Survey (1990–2002) estimated that it occurs in 1 in every 2,289 live births in the United States.<sup>4</sup> The disease appears to be more common in African American women.<sup>1</sup> The rate varies in other populations: it is highest in Haiti, with 1 case in 300 live births, which is nearly 10 times higher than in the United States.<sup>5</sup> The reason for such a variation remains unclear.

Although early reports suggested the death rate was nearly 50%, more recent reports show it to be 0 to 5% in the United States, and the higher numbers in the earlier reports likely represented publication bias.<sup>5,6–9</sup>

## WHAT CAUSES IT?

Peripartum cardiomyopathy is generally considered a form of idiopathic primary myocardial disease associated with the pregnant state. Although several plausible etiologic mechanisms have been suggested, none of them is definite. Some are discussed below.

### Myocarditis

Myocarditis has been found on endomyocardial biopsy of the right ventricle in patients with peripartum cardiomyopathy,<sup>10,11</sup> with a dense lymphocytic infiltrate and variable amounts of myocyte edema, necrosis, and fibrosis. The prevalence of myocarditis in patients with peripartum cardiomyopathy ranged from 8.8% to 78% in different studies.<sup>12,13</sup> On the other hand, the presence or absence of myocarditis alone does not predict the outcome of peripartum cardiomyopathy.<sup>7</sup>

### Cardiotropic viral infections

After a viral infection, a pathologic immune response might occur that is inappropriately directed against native cardiac tissue proteins, leading to ventricular dysfunction.

Bultmann et al<sup>14</sup> found parvovirus B19, human herpes virus 6, Epstein-Barr virus, or cytomegalovirus DNA in endomyocardial biopsy specimens from 8 (31%) of 26 patients with peripartum cardiomyopathy that was associated immunohistologically with interstitial inflammation.

Kühl et al<sup>15</sup> found, in patients with viral infection confirmed by endomyocardial biopsy, that the median left ventricular ejection fraction improved in those in whom the virus was cleared (from 50.2% before to 58.1% afterward,  $P < .001$ ), whereas it decreased in those in whom the virus persisted (from 54.3% before to 51.4% afterward,  $P < .01$ ).

Lyden and Huber<sup>16</sup> found that mice developed worse myocarditis if they were experimentally infected with coxsackievirus and echovirus during pregnancy than if they were infected while not pregnant.

### Chimerism

In a phenomenon called chimerism, cells from the fetus take up residence in the mother (or vice versa), sometimes provoking an immune response.<sup>17,18</sup>

As reviewed by Ansari et al,<sup>19</sup> the serum from patients with peripartum cardiomyopathy has been found to contain autoantibodies in high titers, which are not present in serum from patients with idiopathic cardiomyopathy. Most of these antibodies are against normal human cardiac tissue proteins of 37, 33, and 25 kD. The peripheral blood in these pa-

tients has a high level of fetal microchimerism in mononuclear cells, an abnormal cytokine profile, and low levels of CD4+ CD25lo regulatory T cells.

Warraich et al,<sup>20</sup> in a study from South Africa, Mozambique, and Haiti, found that the frequencies and reactivities of immunoglobulins were similar in distribution in patients with peripartum cardiomyopathy, irrespective of the geographic location.

### Apoptosis and inflammation

Apoptosis (programmed cell death) of cardiac myocytes occurs in heart failure and may contribute to progressive myocardial dysfunction.<sup>21</sup> Experiments in mice suggest that apoptosis of cardiac myocytes has a role in peripartum cardiomyopathy.<sup>22</sup>

Fas and Fas ligand are cell surface proteins that play a key role in apoptosis. Sliwa et al,<sup>23</sup> in a single-center, prospective, longitudinal study from South Africa, followed 100 patients with peripartum cardiomyopathy for 6 months. During this time 15 patients died, and those who died had significantly higher plasma levels of Fas/Apo-1 ( $P < .05$ ). In the same study, plasma levels of C-reactive protein and tumor necrosis factor alpha (markers of inflammation) were elevated and correlated with higher left ventricular dimensions and lower left ventricular ejection fractions at presentation.

In the Studies of Left Ventricular Dysfunction,<sup>24</sup> circulating levels of tumor necrosis factor alpha and interleukin 6 increased in patients as their functional heart failure classification deteriorated.

### An abnormal hemodynamic response

During pregnancy, blood volume and cardiac output increase. In addition, afterload decreases because of relaxation of vascular smooth muscle. The increases in volume and cardiac output during pregnancy cause transient and reversible hypertrophy of the left ventricle to meet the needs of the mother and fetus. Cardiac output reaches its maximum at around 20 weeks of pregnancy.<sup>25</sup>

The transient left ventricular systolic dysfunction during the third trimester and early postpartum period returns to baseline once the cardiac output decreases.<sup>26,27</sup>

**The death rate in this disease is much lower than previously reported**

### Other possible factors

Other possible etiologic factors include prolactin,<sup>28,29</sup> relaxin,<sup>30</sup> immune complexes,<sup>31</sup> cardiac nitric oxide synthase,<sup>32</sup> immature dendritic cells,<sup>33</sup> cardiac dystrophin,<sup>34</sup> and toll-like receptors.<sup>35</sup>

### WHO IS AT RISK?

Demakis and colleagues<sup>2</sup> suggest the following risk factors for peripartum cardiomyopathy:

- Multiparity
- Advanced maternal age (although the disease can occur at any age, the incidence is higher in women over age 30<sup>36</sup>)
- Multifetal pregnancy
- Preeclampsia
- Gestational hypertension
- African American race.

### CLINICAL FEATURES

Peripartum cardiomyopathy involves left ventricular systolic dysfunction in women with no history of heart disease. It can be diagnosed only if other causes of cardiomyopathy are absent.<sup>2</sup>

**Diagnostic criteria** for peripartum cardiomyopathy (all must be present) are<sup>37</sup>:

- Cardiac failure developing in the last month of pregnancy or within 5 months of delivery
- No identifiable cause of the cardiac failure
- No recognizable heart disease before the last month of pregnancy
- An ejection fraction of less than 45%, or the combination of an M-mode fractional shortening of less than 30% and an end-diastolic dimension greater than 2.7 cm/m<sup>2</sup>.

**Symptoms of heart failure** such as dyspnea, dizziness, pedal edema, and orthopnea can occur even in normal pregnancies. Therefore, a pregnant woman in whom peripartum cardiomyopathy is developing may consider her symptoms to be normal. The dyspnea during normal pregnancy is thought to be due to hyperventilation caused by the effects of progesterone, and also due to pressure on the diaphragm from the growing uterus.<sup>38</sup> Peripheral edema occurs in approximately two-thirds of healthy pregnant women.<sup>39</sup> Nevertheless, if swelling and other heart failure symptoms develop suddenly

in an otherwise normal pregnancy, this should prompt further investigation.<sup>40</sup>

Pulmonary edema was a presenting symptom in all 106 patients in a 2007 study in China.<sup>41</sup> The clinical presentation was similar to that of congestive heart failure but was highly variable; 17% of cases were diagnosed antepartum and 83% postpartum. The mean age at diagnosis was 28 ± 6 years. Left ventricular function almost completely normalized in 51% of surviving patients. These findings were similar to those in earlier studies.<sup>2,36</sup> Interestingly, the left ventricular ejection fraction normalized only in 23% of an African cohort.<sup>23</sup>

**Thromboembolism** can be a presentation of peripartum cardiomyopathy. Hemoptysis and pleuritic chest pain may be presenting symptoms of pulmonary embolism.<sup>42</sup>

**Cardiac arrhythmias** and sudden cardiac arrest have also been reported.<sup>43</sup>

**A latent form** of peripartum cardiomyopathy without significant clinical signs and symptoms has been reported.<sup>8</sup>

**Preeclampsia should be excluded** on the basis of history and physical examination, as its management is different. Preeclampsia occurs after 20 weeks of gestation and is characterized by high blood pressure, protein in the urine, swelling, sudden weight gain, headaches, and changes in vision.

**Delayed diagnosis may be associated with higher rates of illness and death;** therefore, physicians should consider peripartum cardiomyopathy in any peripartum patient with unexplained symptoms. Although the symptoms of heart failure can be difficult to differentiate from those of late pregnancy, a heightened suspicion can help.<sup>44</sup>

The aims during the diagnosis are to exclude other causes of cardiomyopathy and to confirm left ventricular systolic dysfunction by echocardiography. Whether endomyocardial biopsy should be done in this setting is still controversial, and recent guidelines do not recommend it.<sup>45,46</sup>

### Role of cardiac MRI

Magnetic resonance imaging (MRI) may be used as a complementary tool to diagnose peripartum cardiomyopathy, and it may prove to be important in identifying the mechanisms involved. It can measure global and segmental

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myocardial contraction, and it can characterize the myocardium.<sup>47</sup>

Furthermore, delayed contrast enhancement (with gadolinium) can help differentiate the type of myocyte necrosis, ie, myocarditis vs ischemia. Myocarditis has a nonvascular distribution in the subepicardium with a nodular or band-like pattern, whereas ischemia has a vascular distribution in a subendocardial or transmural location.<sup>48</sup>

Kawano et al<sup>49</sup> described a patient with peripartum cardiomyopathy whose myocardial damage was demonstrated by delayed contrast enhancement of the left ventricle. This measure improved after she was treated with a beta-blocker, an angiotensin receptor blocker (ARB), and spironolactone (Aldactone), and her cardiac function recovered.

Leurent et al<sup>50</sup> advocate using cardiac MRI to guide biopsy to the abnormal area, which may be much more useful than blind biopsy.

Questions remaining about MRI include the pathologic and prognostic implications of late gadolinium enhancement.

**MANAGEMENT OF POSTPARTUM CARDIOMYOPATHY**

**Heart failure treatment during pregnancy**

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

**Angiotensin-converting enzyme (ACE) inhibitors and ARBs are contraindicated in pregnancy** because they can cause birth defects, although they are the main treatments for postpartum women with heart failure. The teratogenic effects occur particularly in the second and third trimester, with fetopathy characterized by fetal hypotension, oligohydramnios-anuria, and renal tubular dysplasia.<sup>51,52</sup> However, a recent study suggested a risk of malformations even after first-trimester exposure to ACE inhibitors.<sup>53</sup>

**Digoxin, beta-blockers, loop diuretics, and drugs that reduce afterload** such as hydralazine and nitrates have been proven to be safe and are the mainstays of medical therapy of heart failure during pregnancy.<sup>44</sup>

Beta-blockers have strong evidence of efficacy in patients with heart failure, but they have not been tested in peripartum cardiomyopathy. Nevertheless, beta-blockers have long been used in pregnant women with hypertension without any known adverse effects on the fetus, and patients taking these agents prior to diagnosis can continue to use them safely.<sup>46,54</sup>

**Heart failure treatment postpartum**

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

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

**Diuretics** are given for symptom relief.

**Spironolactone or digoxin** is used in patients who have New York Heart Association class III or IV symptoms. The goal with spironolactone is 25 mg/day after dosing of other drugs is maximized. The goal with digoxin is the lowest daily dose to obtain a detectable serum digoxin level, which should be kept at less than 1.0 ng/mL. In the Digitalis Investigation Group trial,<sup>55</sup> serum digoxin levels of 0.5 to 0.8 ng/mL (0.6–1.0 nmol/L) were most beneficial, and levels of 1.1 to 1.5 ng/mL (1.4–1.9 nmol/L) were associated with an increase in deaths related to heart failure.

**Beta-blockers** are recommended for peripartum cardiomyopathy,<sup>44</sup> as they improve symptoms, ejection fraction, and survival. Nonselective beta-blockers such as carvedilol (Coreg) and selective ones such as metoprolol succinate (Toprol XL) have shown benefit. The goal dosage is carvedilol 25 mg twice a day (50 mg twice a day for larger patients) or metoprolol succinate 100 mg once a day.

**Anticoagulation treatment**

During pregnancy, the risk of thromboembolic complications increases due to higher concentrations of coagulation factors II, VII, VIII, and X, and of plasma fibrinogen. The risk may persist up to 6 weeks postpartum.<sup>1</sup> Cases of arterial, venous, and cardiac thrombosis have been reported in women with peripartum cardiomyopathy, and the risk may be related to the degree of chamber enlargement and systolic dysfunction and the presence of atrial fibrillation.<sup>56,57</sup>

Patients with evidence of systemic embolism, with severe left ventricular dysfunction or documented cardiac thrombosis, should receive anticoagulation.<sup>56-58</sup> Anticoagulation should be continued until a return of normal left ventricular function is documented.

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

Warfarin can cause spontaneous fetal cerebral hemorrhage in the second and third trimesters and therefore is generally contraindicated during pregnancy.<sup>59,60</sup> However, guidelines from the American College of Cardiology and the American Heart Association on the management of patients with heart valve disease say that “warfarin is probably safe during the first 6 weeks of gestation, but there is a risk of embryopathy if the warfarin is taken between 6 and 12 weeks of gestation.”<sup>61</sup> The guidelines also say warfarin is “relatively safe” during the second and third trimesters but must be stopped and switched to a heparin several weeks before delivery. Unfractionated heparin or low-molecular-weight heparin can be used during pregnancy. However, should warfarin be needed for any reason, we believe a cesarian section should be performed to reduce the risk to the infant.

### Cardiac transplantation

Patients with severe heart failure despite maximal drug therapy need cardiac transplantation to survive and to improve their quality of life. However, fewer than 3,000 hearts are available for transplantation worldwide per year. Therefore, ventricular assist devices are indicated as a bridge to transplantation.<sup>62</sup>

Patients with symptomatic ventricular arrhythmias should be considered for defibrillator implantation.<sup>63</sup>

### New treatments

**Pentoxifylline** improved outcomes, left ventricular function, and symptoms when added to conventional therapy in a small prospective study.<sup>64</sup>

**Intravenous immunoglobulin** improved the ejection fraction in several studies<sup>65,66</sup> and also markedly reduced the levels of inflamma-

tory cytokines, namely thioredoxin.<sup>67</sup>

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

Investigators have emphasized the need to rule out viral infection before starting immunosuppressive treatment, as the treatment may activate a latent virus, with subsequent deterioration in myocardial function.<sup>28,68</sup>

**Bromocriptine** (Parlodel). Peripartum cardiomyopathy develops in mice bred to have a cardiomyocyte-specific deletion of stat3, leading to enhanced expression and activity of cardiac cathepsin D and promoting the formation of a 16-kD proapoptotic form of prolactin.<sup>29</sup> Therefore, drugs that inhibit prolactin secretion may represent a novel therapy for peripartum cardiomyopathy. Based on this concept, two patients with peripartum cardiomyopathy were treated with bromocriptine, an inhibitor of prolactin secretion, and they showed a good recovery.<sup>69</sup> We require large prospective randomized controlled studies to prove the beneficial effect of blocking prolactin in patients with peripartum cardiomyopathy.

**Other proposed therapies** are calcium channel antagonists,<sup>70</sup> statins,<sup>71</sup> monoclonal antibodies,<sup>72</sup> interferon beta,<sup>73</sup> immunoadsorption,<sup>74</sup> therapeutic apheresis,<sup>75</sup> and cardiomyoplasty.<sup>76</sup>

### How long to treat?

Patients with peripartum cardiomyopathy who recover normal left ventricular function at rest or with low-dose dobutamine (Dobutrex) can be allowed to taper and then discontinue heart failure treatment in 6 to 12 months.<sup>46</sup>

### ■ NATURAL COURSE

In a study of patients with various types of cardiomyopathy, those with peripartum cardiomyopathy had a substantially better prognosis, with a 94% survival rate at 5 years.<sup>7</sup>

Although various reports have shown that the clinical course of peripartum cardio-

**Suspect peripartum cardiomyopathy in any peripartum patient with unexplained symptoms of heart failure**

**In pregnancy, we must also consider the welfare of the fetus**

myopathy is usually related to the return of heart size to normal within 6 months, it is possible that left ventricular function may continue to recover beyond 6 months, and further studies are needed to determine the reasons for this.<sup>54</sup>

Elkayam et al<sup>36</sup> reported that, of 100 patients with peripartum cardiomyopathy in the United States, at the end of 2 years, 9 had died and 4 had received a heart transplant. However, 54 had recovered normal left ventricular function, and recovery was more likely in those with an ejection fraction greater than 30% at diagnosis. The incidence of gestational hypertension was 43%, and the rate of twin pregnancy was 13%. The rate of cesarean delivery was 40%, compared with the national rate of 30.2%.

In contrast, in 98 patients in Haiti, the death rate was 15.3% during a mean follow-up of 2.2 years, and only about 28% had regained normal left ventricular function at 6 months.<sup>5</sup>

**PROGNOSTIC FACTORS**

**Troponin T.** Hu et al<sup>41</sup> reported that the serum cardiac troponin T concentration measured 2 weeks after the onset of peripartum cardiomyopathy correlated inversely with the left ventricular ejection fraction at 6 months. However, the sensitivity was low: a troponin T concentration of more than 0.04 ng/mL predicted persistent left ventricular dysfunction with a sensitivity of only 55%. The specificity was 91%.

**QRS duration** of 120 ms or more has been identified as a predictor of death. Prolonged QRS duration has been shown to be an independent risk factor for death and sudden death in a large series of patients with ischemic and nonischemic cardiac failure.<sup>77</sup>

**Heart dimensions and ejection fraction** had prognostic value in several studies.

Factors predicting normalization of left ventricular function were an initial left ventricular end-systolic dimension of 5.5 cm or less<sup>78</sup> and a left ventricular ejection fraction greater than 27%<sup>78</sup> or 30%.<sup>36</sup>

In a retrospective study,<sup>79</sup> a fractional shortening of 20% or more and a left ventricular end-diastolic dimension of 6 cm or more at

the time of diagnosis increased the risk of persistent left ventricular dysfunction threefold. Other factors at initial assessment associated with lack of recovery were a left ventricular end-diastolic dimension greater than 5.6 cm, left ventricular thrombus, and African American race.<sup>6</sup>

**RISK OF RELAPSE**

Even after full recovery of left ventricular function, subsequent pregnancies carry a risk of relapse of peripartum cardiomyopathy. A study in Haiti followed 99 patients, 15 of whom became pregnant again. Eight of the women who became pregnant again experienced worsening heart failure and long-term systolic dysfunction.<sup>80</sup>

Of six South African women who had New York Heart Association class I symptoms who became pregnant again, two died within 8 weeks of delivery, and the other four continued to have heart failure symptoms.<sup>81</sup>

In the United States, Elkayam et al<sup>82</sup> identified 44 women with peripartum cardiomyopathy who became pregnant again. Of these, 28 had recovered systolic function, with ejection fractions of 50% or higher before becoming pregnant again, and 16 had not. The ejection fraction fell in both groups during the subsequent pregnancy, but in the first group it fell by more than 20% in only 6 (21%), and none died. In contrast, in the second group it fell by more than 20% in 5 (31%), and 3 (19%) died.

Patients who recover normal left ventricular function and have normal left ventricular contractile reserve after dobutamine challenge may undertake another pregnancy safely, but they should be warned of the risk of recurrence even with fully recovered left ventricular function.<sup>46,82</sup>

Dorbala et al<sup>83</sup> performed dobutamine stress echocardiography to measure maximal inotropic contractile reserve in six women presenting with peripartum cardiomyopathy, and it correlated accurately with subsequent recovery of left ventricular function.

Based on these data, our recommendations for further pregnancies are the following:

- If left ventricular function has recovered fully, subsequent pregnancy is not contraindicated, but the patient should be

told that, although the risk is low, it is not absent.

- If left ventricular function has recovered partially, perform dobutamine stress echocardiography. If the left ventricular inotropic response to dobutamine is normal, then patients can be counseled as

above; if the left ventricular inotropic response to dobutamine is abnormal, then the risk is moderate and pregnancy is not recommended.

- If left ventricular function has not recovered at all, the risk is high, and subsequent pregnancy is not recommended. ■

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