REVIEW ARTICLE

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Peripartum Cardiomyopathy

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Peripartum cardiomyopathy is a form of acute and sometimes severe cardiac degeneration that leads to clinical heart failure during pregnancy or in the early postpartum period. The disorder is generally defined as maternal heart failure with systolic dysfunction (left ventricular ejection fraction, <45%) that develops in the last month of pregnancy or in the first 5 months after delivery, in the absence of known preexisting cardiac dysfunction.[1,2] In some cases, however, the disease occurs earlier in pregnancy or more than 5 months after delivery.[3-5]

Peripartum cardiomyopathy complicates approximately 1 in 2000 births worldwide, with substantial variation among regions,[6] including rates as high as 1 in 300 births in Haiti[7] and 1 in 100 in parts of Nigeria.[8] In the United States, the disease is four times as likely to develop in Black women as it is in White women. One third to one half of cases occur in women with hypertensive diseases of pregnancy, including preeclampsia.[9-11] Other strong risk factors for peripartum cardiomyopathy include multiple gestations, advanced maternal age, and anemia. The mode of delivery, such as cesarean section, is not recognized as a risk factor.

Peripartum cardiomyopathy is now a leading cause of maternal death in many parts of the United States and around the world.[12-14] Approximately 60% of cases of cardiogenic shock during pregnancy or in the early postpartum period are caused by peripartum cardiomyopathy.[15] Although cardiac function typically recovers in more than 50% of affected patients, morbidity and mortality are nevertheless high, with some patients requiring a left ventricular assist device (LVAD) or cardiac transplantation. Black women in the United States are twice as likely as White women to have persistently impaired heart function, and among Black women in whom heart function does recover, it takes twice as long to do so.[16] Mortality rates are as high as 20%, and the rates are highest among Black women in the United States and among women in less developed countries worldwide.[17] Peripartum cardiomyopathy can thus be devastating at a critical time in the lives of affected persons, their families, and their newborn children.

Clinical Presentation and Evaluation

Patients with peripartum cardiomyopathy typically present with symptoms and signs of heart failure, including dyspnea, orthopnea, elevated jugular venous pressure, pulmonary rales, and edema. The diagnosis requires a high index of suspicion and is often delayed because symptoms mirror those of pregnancy itself. The presentation of peripartum cardiomyopathy can also be accelerated and even catastrophic, including cardiogenic shock. Infrequently, affected persons present with a complication of the disease, such as an arrhythmia or a thromboembolic event. Sixty to ninety percent of cases of peripartum cardiomyopathy occur after delivery,

with the highest incidence in the first postpartum week, although there is substantial geographic variation in the timing of presentation.[5] In the United States, Black women are more likely than White women to present later in the postpartum period, perhaps in part accounting for the poorer outcomes in this group.[4]

Peripartum cardiomyopathy is a diagnosis of exclusion. The differential diagnosis includes preexisting structural heart disease, preeclampsia-induced pulmonary edema in the absence of systolic dysfunction, pulmonary embolism, spontaneous coronary artery dissection, and exposure to toxins, including alcohol and chemotherapeutic agents (Table 1). The diagnosis of peripartum cardiomyopathy is generally made by means of echocardiography, with documentation of systolic dysfunction in the absence of other structural heart disease.[1,18] Left ventricular dilatation is common but not always seen. Findings such as sinus tachycardia on the electrocardiogram and pulmonary venous congestion on a chest radiograph are typically nonspecific. Endomyocardial biopsy is usually not needed to diagnose peripartum cardiomyopathy and is rarely performed. Magnetic resonance imaging (MRI) can be helpful in evaluating systolic function and cardiac structure. Although levels of plasma brain natriuretic peptide do not change substantially during a normal pregnancy, they are usually elevated in patients with peripartum cardiomyopathy, a finding that can prompt a consideration of this diagnosis.[1,18] Currently, there is no biomarker that is diagnostic for peripartum cardiomyopathy. Genetic testing is increasingly offered to patients with peripartum cardiomyopathy, and it should be considered in most cases.[19]

Table 1. Differential Diagnosis of Peripartum Cardiomyopathy.*

Differential Diagnosis	Differentiating Markers
Preexisting cardiomyopathy	History, family history, prior echocardiography
Preeclampsia-induced pulmonary edema in the absence of systolic dysfunction	History, preserved ejection fraction on echocardiography, sFlt-1 and PLGF levels
Pulmonary or amniotic embolism	History, chest CT
Valvular heart disease, including rheumatic disease	History, echocardiography
Congenital heart disease that has resulted in surgical correction	History, echocardiography
Chemotherapy-induced cardiomyopathy	History, especially of treatment with doxorubicin or other anthracyclines, trastuzumab, or sorafenib
Spontaneous coronary-artery dissection	History, echocardiography, elevated troponin levels
Other causes of myocardial infarction, including MINOCA	History, echocardiography, elevated troponin levels
Myocarditis, including giant-cell myocarditis	History, endomyocardial biopsy
Takotsubo cardiomyopathy	History, apical ballooning on echocardiography
Tachycardia-induced cardiomyopathy	History, especially atrial fibrillation
Pulmonary edema resulting from prolonged tocolysis	History, preserved ejection fraction on echocardiography
Sepsis, thyrotoxicosis, and other high-output causes of heart failure	History, high output on echocardiography
Aortic dissection	History, findings on CT angiogram

* CT denotes computed tomography, MINOCA myocardial infarction with no obstructive coronary artery disease, PLGF placental growth factor, and sFlt-1 soluble fms-like tyrosine kinase 1.

PATHOGENESIS

The causes of peripartum cardiomyopathy remain poorly understood. Pregnancy increases maternal blood volume, cardiac output, and cardiac mass beginning in the second trimester of gestation.[20] Peripartum cardiomyopathy has thus often been proposed to represent a failed hemodynamic stress test. However, the disorder typically develops after delivery, and systolic function appears to be preserved earlier during gestation.[21] The onset of peripartum cardiomyopathy is thus temporally discordant with the hemodynamic changes of pregnancy (Fig. 1). Myocarditis has also been suggested to cause peripartum cardiomyopathy, but endomyocardial biopsy specimens from patients with peripartum cardiomyopathy do not appear to contain any more viral genomes that have been implicated in myocarditis than do control specimens,[22] and cardiovascular MRI studies with late gadolinium enhancement in women with peripartum cardiomyopathy of recent onset rarely reveal evidence of myocarditis.[23]

Over the past few years, an alternative model of the pathogenesis of peripartum cardiomyopathy has emerged. Studies have suggested that the disorder is triggered by hormones that ema-

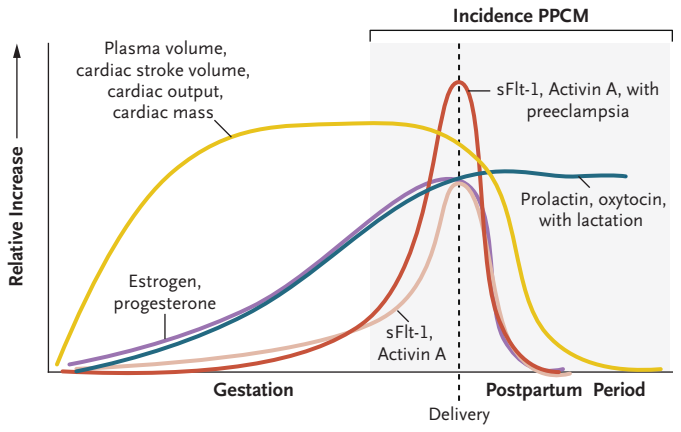

Figure 1. Temporal Hormonal and Hemodynamic Changes during Pregnancy in Relation to the Incidence of Peripartum Cardiomyopathy (PPCM).

Hemodynamic changes of pregnancy, including increases in plasma volume and cardiac stroke volume, cardiac output, and cardiac mass, occur during early gestation; these changes are temporally discordant with the typical postpartum presentation of PPCM. Late gestation and the postpartum period are also characterized by profound changes in hormones. The abbreviation sFlt-1 denotes soluble fms-like tyrosine kinase 1.

nate from the pituitary and placenta during the peripartum period, synergizing, in ways still poorly understood, with intrinsic cardiac factors that render some women susceptible to these hormonal imbalances. Hormones produced by the pituitary and the placenta normally modulate maternal physiology to support fetal and newborn growth and development (Fig. 1). Under certain circumstances, however, some of these processes can lead to cardiac dysfunction (Fig. 2). For example, prolactin, secreted from the pituitary in late gestation and after delivery in lactating persons, was shown in mouse models of peripartum cardiomyopathy to be cleaved to a breakdown product that damages the cardiac vasculature. The damaged vessels, in turn, trigger ventricular systolic dysfunction through a combination of cardiac ischemia and paracrine signaling, including the secretion by endothelial cells of exosomes containing microRNAs (miRNAs) that, when taken up by cardiomyocytes, promote cardiomyocyte apoptosis.[24,25] These observations have suggested that suppression of prolactin secretion, either by pharmacologic means or by cessation of breast-feeding, may be beneficial in patients with peripartum cardiomyopathy. Oxytocin, which is secreted by the pituitary to promote lactation, can also have vasculotoxic effects, promoting postpartum aortic dissection in models of Marfan's syndrome,[26] but a definitive role in peripartum cardiomyopathy has not been directly established.

The human placenta is also intensely secretory in late gestation. Syncytiotrophoblasts produce glycoprotein hormones, growth hormones, metallopeptidases, steroids, neuropeptides (despite the absence of neurons), and senescence-associated secretory proteins.[27] Soluble fms-like tyrosine kinase 1 (sFlt-1), a soluble decoy receptor for vascular endothelial growth factor that is abundantly secreted by the placenta in late gestation, has been shown to trigger cardiovascular rarefaction, leading to peripartum cardiomyopathy in mice.[28] The latter observation may explain the strong epidemiologic associations of preeclampsia and multiple gestations with peripartum cardiomyopathy, because large increases in placental secretion of sFlt-1 are seen in both contexts.[29] In fact, subclinical cardiac dysfunction can be detected in patients with preeclampsia even in the absence of peripartum cardiomyopathy, and the extent of dysfunction correlates with levels of circulating sFlt-1.[30]

Numerous other peptide hormones secreted by the late-gestation, senescing placenta, including activin A, are likely to contribute directly to cardiomyocyte dysfunction.[31] Peripartum levels of activin A in women with preeclampsia, like sFlt-1 levels, correlate with subclinical cardiac dysfunction, including 1 year after delivery.[32] The late-gestation placenta is also abundantly steroidogenic. Progesterone, highly secreted by the placenta, suppresses the burning of carbohydrates by the heart, promotes cardiac hypertrophy, and may have direct negative-inotropic effects, all of which probably sensitize the heart to further insults.[33-35] Conversely, secretion of some pregnancy-associated vasculoprotective hormones, such as relaxin-2, are suppressed in patients with peripartum cardiomyopathy.[36,37] Together, these studies of pregnancy hormones have suggested a vasculohormonal model of the pathogenesis of peripartum cardiomyopathy, whereby imbalances in peripartum hormones cause cardiovascular dysfunction and consequent heart failure in susceptible women.[38]

What intrinsic cardiac factors render some

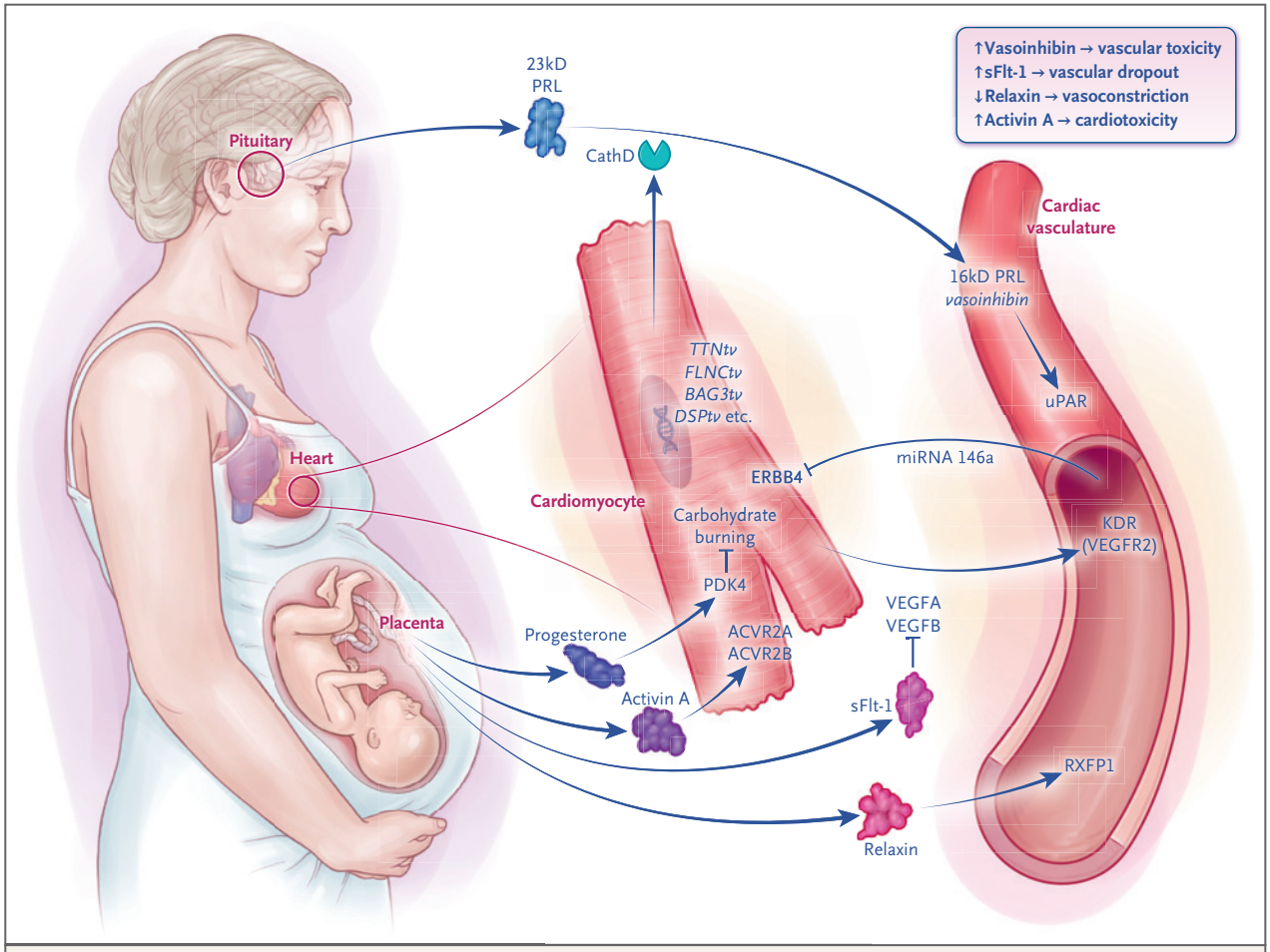

Figure 2. Hormonal Model of PPCM.

Hormones secreted from the pituitary and the placenta affect cardiac vasculature and function. Prolactin (PRL), secreted by the pituitary during lactation, can be converted by cathepsin D (CathD), secreted by cardiomyocytes, to a vasoinhibin, which acts on the urokinase-type plasminogen activator receptor (uPAR) to inhibit vascular function and promote vascular secretion of vesicles containing microRNA (miRNA) 146a. These vesicles transduce cardiomyocytes to suppress prosurvival signaling by Erb-B2 receptor tyrosine kinase 4 (ERBB4). As a decoy receptor for vascular endothelial growth factor (VEGF), sFlt-1 is secreted by the placenta and potently suppresses provascular signaling by VEGF. Activin A, also secreted by the placenta, directly affects cardiomyocyte function through activin receptor type 2 (ACVR2). Progesterone, largely secreted by the placenta in late gestation, induces pyruvate dehydrogenase kinase 4 (PDK4) in cardiomyocytes, suppressing carbohydrate oxidation by the heart and sparing glucose for fetal use but also resulting in a cardiac vulnerability. Placental secretion of both sFlt-1 and activin A is accentuated in patients with preeclampsia. Relaxin, secreted by the corpus luteum early in pregnancy and by the placenta late in pregnancy, promotes vascular health through multiple mechanisms. Relaxin levels are reduced in patients with PPCM.

women but not others susceptible to these hormonal imbalances? This question remains largely unanswered, but recent studies have revealed a strong genetic predisposition to peripartum cardiomyopathy in some cases (Table 2). Approximately 15% of women with peripartum cardiomyopathy have heterozygous loss-of-function genetic variants in one of several genes known to be associated with nonischemic dilated cardiomyopathy, a disease that in part resembles peripartum cardiomyopathy.[39,40] The frequencies of identified variants in dilated cardiomyopathy and in peripartum cardiomyopathy are nearly identical, suggesting that these two diseases may lie on a spectrum, reflecting different environmental insults superimposed on

Table 2. Prevalence of Rare Loss-of-Function Genetic Variants in Patients with Peripartum Cardiomyopathy (PPCM) or Dilated Cardiomyopathy (DCM).*

Gene	Protein	Prevalence in PPCM	Prevalence in DCM
		percent	
TTN	Titin: large protein that spans the sarcomere	10.5	11.3
DSP	Desmoplakin: desmosomal protein critical for cell junctions	1.3	1.4
FLNC	Filamin C: actin-binding protein at the Z disk	0.8	3.0
MYH7	Myosin heavy chain 7: contractile component of sarcomere	0.4	0.2
MYH6	Myosin heavy chain 6: cardiac-specific sarcomeric protein	0.4	0.3
BAG3	Regulator of chaperone-assisted selective autophagy	0.2	0.3
FKTN	Fukutin: regulates α-dystroglycan glycosylation	0.2	0.2
VCL	Vinculin: transmits force from cytoplasmic actin to membrane integrins	0.2	0.1

* The information presented in the table is from Goli et al.[39]

the background of a similar genetic predisposition to disease. But how the genetic predisposition synergizes with the hormonal changes discussed above remains unclear. Cardiomyopathy caused by chemotherapeutic agents[41] or by alcohol consumption[42] is also more frequent among persons with some of these variants, which suggests a common yet unidentified pathophysiology.

Two thirds of the identified genetic variants in both women with peripartum cardiomyopathy and patients with dilated cardiomyopathy lie in *TTN*, the gene encoding the large sarcomeric protein, titin.[39] How variants in *TTN* cause disease also remains uncertain, although recent work has shown that the encoded truncated titin proteins are expressed and detectable in failing hearts.[43,44] The penetrance of *TTN* loss-of-function variants that cause disease is less than 5%,[45] a finding that is consistent with the notion that other, unknown factors, genetic and environmental, contribute to the pathogenesis of cardiomyopathy. Only about 100 genes have thus far undergone targeted sequencing in cohorts of women with peripartum cardiomyopathy, and data on the landscape of common variants in peripartum cardiomyopathy are limited.[46,47] Potentially causal variants in other genes thus await discovery.

Other pathogenic contributors to peripartum cardiomyopathy have been proposed, including autoimmunity[48] and microchimerism,[49] although the supportive data for these mechanisms are limited. Biomarker studies,[50] including recent proteomic analysis in human cohorts,[51] have suggested a role of inflammation in peripartum cardiomyopathy, but whether these inflammatory signatures reflect the course of disease or contribute to its progression is not clear, and the answer will require further research. Selenium deficiency appears to contribute to peripartum cardiomyopathy in some parts of Nigeria, through unknown mechanisms,[52,53] but selenium deficiency is rare in most other areas of the world and thus is not likely to contribute to peripartum cardiomyopathy generally.

MANAGEMENT AND OUTCOMES

Few randomized trials have evaluated therapies for peripartum cardiomyopathy, and none of these studies have had conclusive results. Current management is thus largely extrapolated from guideline-directed medical treatment for nonischemic dilated cardiomyopathy and other forms of heart failure with a reduced ejection fraction.[1,54] Diuretics and nitrates are used to control volume, but caution is required to avoid hypotension if they are used before delivery. Neurohormonal blockade with angiotensin-converting–enzyme inhibitors, angiotensin II receptor blockers, and aldosterone receptor antago-

nists can be administered after delivery but are contraindicated before delivery. Hydralazine plus isosorbide dinitrate is an alternative regimen for afterload reduction during pregnancy. Beta-blockers are routinely indicated and are safe during pregnancy. There are no data on the safety and use, either during or after pregnancy, of more recently developed pharmaceutical agents for heart failure with a reduced ejection fraction, including sacubitril–valsartan and sodium–glucose cotransporter 2 inhibitors, but these agents are increasingly used after delivery in patients with peripartum cardiomyopathy, on the basis of extrapolation from guideline-directed medical treatment for dilated cardiomyopathy and other forms of heart failure with a reduced ejection fraction. Most standard heart failure medications are compatible with breast-feeding, but no safety information is available for the newer agents.

Advanced therapies are used as needed, including mechanical circulatory support with an intra-aortic balloon pump, percutaneous ventricular assist devices, extracorporeal membrane oxygenation, and LVADs. There is some evidence, however, that adrenergic support may be deleterious.[55] In general, aggressive treatment is often appropriate, given the young age of the patients and the frequent recovery of cardiac function.

Several aspects of the management of peripartum cardiomyopathy, as compared with the management of other forms of heart failure with a reduced ejection fraction, warrant special consideration. The hypercoagulable state of pregnancy, especially the peripartum period, increases the risk of thrombotic complications, including left ventricular thrombus and thromboembolic events, which occur in 5 to 20% of cases.[56,57] The threshold for initiating anticoagulant therapy should therefore be low — for example, an ejection fraction of less than 30 to 35% or the presence of atrial fibrillation. Ventricular arrhythmias are common in patients with peripartum cardiomyopathy, and when a defibrillator is indicated, use of a temporary, wearable defibrillator should be considered instead of an implantable cardioverter–defibrillator because cardiac contractility often recovers.[58,59]

Management of labor and delivery in patients with peripartum cardiomyopathy during gestation can be complex and should be carried out by a multidisciplinary team that includes an obstetrician with expertise in maternal–fetal medicine, an anesthesiologist, a cardiologist, and a specialist in advanced heart failure, especially when the patient is hemodynamically unstable. Patients who are hemodynamically stable can deliver vaginally. Lactation is generally not contraindicated. There are no proven disease-specific therapies for peripartum cardiomyopathy, but the use of bromocriptine to suppress the release of prolactin from the pituitary is currently under investigation and may be considered in patients with a left ventricular ejection fraction of less than 35%.

A referral for genetic counseling and testing should be considered, even in the absence of a family history of peripartum cardiomyopathy or dilated cardiomyopathy.[19,60] The presence of pathogenic variants in *TTN* does not presage a different prognosis, but variants in filamin C (*FLNC*) and desmoplakin (*DSP*) are associated with ventricular arrhythmias in patients with dilated cardiomyopathy, and the same may be true in patients with peripartum cardiomyopathy.[39] Peripartum cardiomyopathy can also be the first presentation of rare diseases such as Danon's disease (*LAMP2* variants) or Duchenne's muscular dystrophy (*DMD* variants).[40] When a pathogenic variant is identified, cascade testing of family members may be beneficial in order to provide reassurance and obviate the need for close monitoring during pregnancy in relatives who do not carry the variant identified in the proband.

Clinical outcomes for patients with peripartum cardiomyopathy vary widely and are generally better in developed countries.[5] In most women, the left ventricular ejection fraction increases to more than 50% within 6 months after diagnosis, but in many women, a return to normal cardiac function takes longer, and in some women, cardiac function never fully recovers.[61,62] Implantation of an LVAD or heart transplantation is required in up to 10% of cases, and survival among transplant recipients is inferior to survival among age-adjusted patients who received heart transplants for other reasons.[63,64] Overall, mortality among patients with peripartum cardiomyopathy can be as high as 20%, and

it is higher in low-income countries than in high-income countries, despite a generally lower incidence of known risk factors in low-income countries.[11,17,65] A lower left ventricular ejection fraction at presentation most strongly correlates with persistent systolic dysfunction but does not have a high predictive value. Other indicators of adverse outcomes include a late presentation (more than 1 week after delivery),[4,61] late gadolinium enhancement on MRI, left ventricular dilatation,[61] and right ventricular dysfunction.[66-69] The occurrence of preeclampsia with peripartum cardiomyopathy has been associated with better left ventricular recovery[70] and with a higher incidence of adverse cardiovascular outcomes.[71]

AREAS OF UNCERTAINTY AND FUTURE DIRECTIONS

The dearth of data from randomized trials of therapies or treatment strategies in patients with peripartum cardiomyopathy and the lack of data from long-term longitudinal studies in this population leave much uncertainty about the management of peripartum cardiomyopathy and the long-term prognosis. Preclinical studies suggest that suppression of prolactin secretion, with the use of the dopamine agonist bromocriptine or by cessation of breast-feeding, may be beneficial. However, clinical data are less clear. A small, open-label trial involving 20 women randomly assigned to receive bromocriptine or placebo suggested a benefit of bromocriptine treatment, but mortality in the control group was high.[72] A larger trial, with 60 women randomly assigned to one of two bromocriptine dosing regimens, revealed no significant differences in the recovery of left ventricular ejection fraction between the regimens, but the trial did not have a placebo control group.[73] A meta-analysis of these two trials and nonrandomized studies pointed to a benefit with bromocriptine treatment.[74] The European Society of Cardiology guidelines suggest that the use of bromocriptine be considered,[75] but there is less consensus among U.S. experts. The ongoing Randomized Evaluation of Bromocriptine in Myocardial Recovery Therapy for Peripartum Cardiomyopathy (REBIRTH), a trial involving 200 women randomly assigned to receive bromocriptine or placebo (ClinicalTrials.gov number, NCT05180773) is expected to be completed in 2026, and the results may resolve the question of whether bromocriptine provides a benefit.

The limited data available to date suggest that breast-feeding is safe in women with peripartum cardiomyopathy.[76,77] Currently, the theoretical benefits of suppressing prolactin, whether with bromocriptine or by cessation of breast-feeding, must therefore be weighed against the benefits of breast-feeding to mother and child. Withholding breast-feeding increases infant mortality by a factor of more than 10 in many parts of the world. The World Health Organization and the American Academy of Pediatrics recommend exclusive breast-feeding for the first 6 months, with continued breast-feeding for up to 2 years.[78]

Counseling patients who are considering a subsequent pregnancy is difficult. The disease recurs in 10 to 50% of cases, and recurrent disease can have worse outcomes, including death.[79-82] Lack of recovery of systolic function before a subsequent pregnancy is associated with worse outcomes but is not a strong predictor. Counseling must therefore weigh uncertain risks with an often strong desire on the part of the patient to expand the family. Careful monitoring by a multidisciplinary team during and after a subsequent pregnancy is likely to improve outcomes.[81,83]

Long-term outcomes (i.e., at >5 years) have not been studied extensively, despite the young age of patients at presentation. The impact of peripartum cardiomyopathy on lifelong mental well-being, including that of family members, appears to be substantial but is understudied. As many as half of women with peripartum cardiomyopathy may meet criteria for mental disorders such as depression or post-traumatic stress disorder.[84,85]

When and how to withdraw medications once systolic function has recovered is also uncertain. Cellular and molecular recovery are likely to lag behind echocardiographic evidence of recovery, and persistent cardiac dysfunction can often be evoked by exercise or dobutamine testing, despite a return to a normal ejection fraction, indicating incomplete recovery.[86,87] Premature withdrawal of medications can precipitate a recurrence in patients with dilated cardiomyopathy, but similar studies in patients with peripar-

tum cardiomyopathy have not been reported.[88] A reasonable approach to withdrawing medications may be to wait for 1 year after echocardiographic studies suggested recovery and to withdraw one medication at a time, with close and long-term clinical and echocardiographic monitoring.[1,18]

Racial disparities in peripartum cardiomyopathy are substantial but poorly understood. In the United States, peripartum cardiomyopathy is more frequent in Black women than in White women, and the outcomes are worse. Studies suggest that socioeconomic factors such as neighborhood deprivation and provider bias, rather than genetic factors, may be driving this inequity,[11,89] but more work is needed in this area. Wider use of diagnostic biomarkers such as brain natriuretic peptide may reduce disparities by preventing delayed diagnoses. Various other potential biomarkers, such as high-sensitivity troponin and miRNAs, as well as evaluation of electrocardiograms with the use of artificial intelligence, are being investigated, but none of these diagnostic approaches are yet sufficiently reliable for clinical use.[25,90-93]

Research into the mechanisms underlying peripartum cardiomyopathy remains challenging. Much research has been done with mice, but the human placenta differs substantially from the murine placenta, which is less invasive and less endocrinologically active[94]; this limits how much can be studied in a murine model.

SUMMARY

Peripartum cardiomyopathy has become an important cause of maternal morbidity and mortality. The pathogenesis of the disorder remains incompletely understood. Genetic studies suggest that peripartum cardiomyopathy may lie on a spectrum with dilated cardiomyopathy, and genetic testing should be offered to patients and families. The neurohormonal changes of late gestation and parturition probably trigger peripartum cardiomyopathy in genetically or otherwise susceptible women. Management of peripartum cardiomyopathy largely mirrors guideline-directed medical treatment for heart failure with a reduced ejection fraction. No disease-specific therapy has proven efficacy to date, but an ongoing randomized trial is evaluating suppression of prolactin as a therapeutic approach. The short-term prognosis for patients with peripartum cardiomyopathy is usually favorable, but a subset of patients fare poorly and face chronic heart failure, a need for heart transplantation, or death. Racial inequities in peripartum cardiomyopathy are profound and poorly understood. Little is known about the long-term outcomes of this disorder.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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