CME

Peripartum Cardiomyopathy

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Peripartum cardiomyopathy is defined by left ventricular dysfunction and development of cardiac failure without a known cause and occurring in the final month of pregnancy and up to 5 months postpartum. Peripartum cardiomyopathy is an important and steadily increasing cause of pregnancy-associated morbidity and mortality. The incidence of peripartum cardiomyopathy in the United States has been estimated recently as 1 in 2,230 births and approximately 1 in 1,000 births worldwide. The etiopathogenesis of peripartum cardiomyopathy remains elusive; however, it is generally thought to be from a two-hit hypothesis in which an underlying cardiomyocyte protein mutation results in apoptosis mediated by vascular and hormonal actions. Clinical recognition is integral to the management of this disease, because there must be careful exclusion of alternative etiologies. Although there are no disease-specific therapies, management of peripartum cardiomyopathy is based on treatment of heart failure and its symptoms, repressing neurohormonal responses, and preventing long-term sequelae. Ventricular function recovery and rates of recurrence of peripartum cardiomyopathy vary by ethnicity and geography. Mortality rates associated with peripartum cardiomyopathy range from 3% to 40%, depending on geographic location. In this review, normal cardiovascular adaptations in pregnancy are summarized and current evidence-based clinical management of the disease is discussed.

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For more than 150 years, peripartum heart failure has both intrigued and terrified obstetric care providers. This morbid curiosity was first reported by Ritchie in 1849 with subsequent descriptions of "an idiopathic myocardial degeneration" by Virchow in 1870 in women who died in the puerperium.[1,2] The contemporary clinical syndrome of "postpartal heart failure" can be traced to the 1930s reports of Gouley and Hull et al.[3] This "toxic" postpartal heart disease, as it was known at the time, was described as congestive heart failure of moderate or extreme severity with symptoms that appeared typically within a month after delivery. Because some reports began to cite the development of cardiac failure in the last month of pregnancy, the term peripartum cardiomyopathy was coined.[1] In 1997, peripartum cardiomyopathy was defined by the National Institutes of Health Workshop convened by the National Heart, Lung, and Blood Institute and the Office of Rare Diseases as the development of cardiac failure in the last month of pregnancy or within 5 months after delivery.[4] Other criteria include an absence of an identifiable cause for cardiac failure, absence of recognizable heart disease before the last month of pregnancy, and left ventricular dysfunction demonstrated by echocardiographic criteria.

Over the past two decades, literature concerning peripartum cardiomyopathy has accrued at a rapid pace. Using the search term "peripartum cardiomyopathy," there were nearly 100 citations in MEDLINE in the year 2017 compared with the isolated reports from the 1970s and early 1980s. Because of this, knowledge of the disease has advanced tremendously. The aim of this report is to both review normal cardiovascular

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adaptations to pregnancy as well as synthesize current understandings of the etiology and management of peripartum cardiomyopathy.

EPIDEMIOLOGY

Significance

The subject of pregnancy-associated cardiovascular disease is currently of considerable interest given the recent reports of its causative role for increasing maternal mortality in the United States.[5,6] In fact, the contribution of the classic threats such as hemorrhage and hypertensive disorders of pregnancy have declined, whereas that of cardiovascular and other medical conditions have increased compared with reports from the mid-2000s.[6] To emphasize, cardiovascular conditions, including peripartum cardiomyopathy, were responsible for 26% of all pregnancy-related deaths in the United States from 2011 to 2013.[6]

Incidence

The reported incidence of peripartum cardiomyopathy varies widely owing to a number of factors. Prominent among these are the geographic vicissitudes of the syndrome. Other factors are differing definitions and evolving diagnostic criteria as noted earlier. Finally, accurate data are lacking because of the paucity of population-based registries.[7] Worldwide, peripartum cardiomyopathy affects approximately 1 per 1,000 pregnancies with geographic hot spots found in Africa–up to 1 per 100 pregnancies–and Haiti–1 in 300 births.[8] In Nigeria, where rates are reported to be as high as 1%, many of the cases likely are the result of pure volume overload caused by the Hausa tradition of ingesting a dried lake salt.[9,10]

These rates differ markedly from those reported in the United States and depend on contemporaneous technology. For example, in an earlier study of 106,000 pregnancies at Parkland Hospital, there were 28 cases of peripartum cardiomyopathy diagnosed initially, but on careful review, three fourths of these women were identified to have previously undiagnosed cardiac disease.[11] These cases were also usually associated with superimposed obstetric complications. Examples such as this report suggested that the incidence of peripartum cardiomyopathy was overestimated during the 1970s and 1980s.[10]

Improved access to echocardiographic technology along with heightened awareness of the diagnosis serve to explain more recent trends showing an increased incidence. In the United States, for example, the incidence of peripartum cardiomyopathy has increased over the past two decades.[12] Other explanations for these rising rates include associated factors such as increasing maternal age, fertility-assisted treatments, and multifetal pregnancies.[8,13] Moreover, obesity has reached epidemic levels during this period and serves as a potent adjunct to pregnancy-associated cardiac dysfunction.[11] Owing to these and other factors, the incidence of peripartum cardiomyopathy in the United States has increased from 1 in 4,350 births in the early 1990s to 1 in 2,230 births in the mid-2000s.[12] Importantly, careful exclusion of alternative etiologies of heart failure are paramount in both defining prevalence in the population and in caring for the individual patient.

CARDIAC PHYSIOLOGY DURING PREGNANCY

Pregnancy-induced hypervolemia is necessary to meet the needs of a prodigious uterine blood flow and fetal perfusion while allowing the mother to function without impairment. This is accomplished by a 30–50% increase in cardiac output that was reported as early as the early 1900s. The gold standard for maternal cardiovascular evaluation is use of flow-directed pulmonary artery catheters with thermodilution methodology. Because of the invasive nature of such techniques, only cross-sectional studies have been feasible. In a landmark study, Clark et al[14] used this technology in healthy pregnant women to assess late pregnancy cardiovascular physiology compared with values measured 3 months postpartum (Table 1). Other technologic advancements, particularly in imaging modalities to include echocardiography and

Table 1. Hemodynamic Changes in 10 Healthy Pregnant Women Without Peripartum Cardiomyopathy at Term Compared With Repeat Values Obtained at 12 Weeks Postpartum

Parameter	Change (%)
Cardiac output (L/min)	+43
Heart rate (bpm)	+17
Left ventricular stroke work index (g/m/m^2)	+17
Vascular resistance (dyn/sec/cm^{-5})	
Systemic	−21
Pulmonary	−34
Mean arterial pressure (mm Hg)	+4
Pulmonary capillary wedge pressure (mm Hg)	+33
Central venous pressure (mm Hg)	0
Colloid osmotic pressure (mm Hg)	−14

bpm, beats per minute.

Data from Clark SL, Cotton DB, Lee W, Bishop C, Hill T, Southwick J, et al. Central hemodynamic assessment of normal term pregnancy. Am J Obstet Gynecol 1989;161:1439-42.

cardiac magnetic resonance imaging, permit serial assessment of cardiac function throughout both normal and abnormal pregnancy.[15]

Hormones secreted by the corpus luteum are thought to orchestrate these early cardiovascular changes.[16] These induce profound changes in systemic vascular resistance and, as early as 5 weeks of gestation, result in substantively decreased systolic and diastolic blood pressures. Importantly, at least half of the total rise in cardiac output during pregnancy has manifested as early as 8 weeks of gestation, whereas mean blood pressure nadirs at 16–20 weeks of gestation, with changes persisting into the third trimester. Because of the reduction in peripheral vascular resistance, stroke volume becomes augmented and increases from early pregnancy until approximately 16 weeks of gestation after which it plateaus along with cardiac output.[15,17]

Despite these dramatic hemodynamic alterations, intrinsic left ventricular contractility does not appear to change appreciably.[14,16] Specifically, normal left ventricular function is maintained during pregnancy, which is not characterized by a high-output cardiac state with hyperdynamic function. The cardiac atria and ventricles must, however, accommodate the pregnancy-induced hypervolemia, which is demonstrated by increased end-systolic and end-diastolic dimensions.[18] Consequently, normal pregnancy is associated with increased left ventricular mass.[19,20] More specifically, there are significant increases in left ventricular mass that are proportional to maternal size. The cardiac atria have a similar increase in mass.[18] Such cardiac remodeling is a normal, physiologic response, and some, but not all, suggest these changes resolve by 3 months postpartum.[17,21]

ASSOCIATED CONDITIONS

There are a number of associated conditions with peripartum cardiomyopathy. One example is advancing maternal age. Although peripartum cardiomyopathy affects women in all age groups, more than half of the cases are in women older than 30 years of age. Indeed, the incidence is 10-fold higher in women older than 40 years old compared with those younger than 20 years old.[22]

Black race is another strongly associated risk factor for the development of peripartum cardiomyopathy.[23] This racial predominance also translates to the previously cited geographic proclivities with incidences as high as 1% in some populations. In the United States, a 5- to 15-fold increased risk for black women compared with other races has been reported.[24]

Pregnancy-associated hypertension, and in particular preeclampsia, strongly predisposes patients to development of peripartum cardiomyopathy.[25] Underlying chronic hypertension also likely plays a role in some women. Depending on the population studied, the incidence of peripartum cardiomyopathy associated with hypertensive disorders of pregnancy is increased from 5- to 30-fold.[22,26] This association is particularly important because it is crucial to make the distinction between permeability pulmonary edema caused by preeclampsia and cardiogenic edema caused by heart failure from peripartum cardiomyopathy.[8] Similarly, differentiating between hypertensive heart failure from underlying ventricular concentric hypertrophy and superimposed preeclampsia is imperative.[11] The pivotal role played by antiangiogenic factors associated with preeclampsia is discussed in detail subsequently. Similarly, it is well known that women with a multifetal pregnancy are more susceptible to development of peripartum cardiomyopathy. In one meta-analysis, 9% of cases of peripartum cardiomyopathy were in women with a multifetal pregnancy.[27] This association is enigmatic until the role of hyperplacentosis and antiangiogenic factors are considered as discussed under "Etiopathogenesis." Importantly, obstetric comorbidities such as obesity, anemia, and infection are common with peripartum cardiomyopathy.[11]

ETIOPATHOGENESIS

Until recently, the etiology and pathophysiology of peripartum cardiomyopathy have been elusive. However, within the past decade, there have been salient observations that have opened new vistas in elucidation of its etiopathogenesis. Some putative causes of peripartum cardiomyopathy are shown in Box 1.

One of the oldest theories is that peripartum cardiomyopathy is simply a failed hemodynamic

Box 1. Possible Causes or Triggering Events for Peripartum Cardiomyopathy

Hemodynamic stress
Viral myocarditis—coxsackievirus, echovirus, parvovirus B19
Microchimerism—myocyte engraftment with immune dysfunction
Genetic factors—mutations of cardiac genes—*TTNC1, TTN, STAT3*
Prolactin—increased cathepsin D peptidase
Antiangiogenic factors—sFlt-1 inhibition of VEGF

sFlt-1, soluble fms-like tyrosine kinase-1; VEGF, vascular endothelial growth factor.

"stress test" of pregnancy. According to this reasoning, the profound effects of pregnancy on cardiovascular physiology shown in Table 1 ultimately lead to peripartum heart failure. This theory is especially problematic in that the bulk of these changes that burden cardiac function are exerted by midpregnancy, and with very few exceptions, peripartum cardiomyopathy is a disease of late pregnancy and the puerperium. Thus, if peripartum cardiomyopathy were a failed stress test, it would be expected to occur much earlier and more often than it does.

A number of earlier studies provided data that viral myocarditis may be a precipitating cause of peripartum cardiomyopathy. These observations came from findings that right-sided endomyocardial biopsies displayed evidence of inflammation. Although polymerase chain reaction studies of biopsy specimens from 30% of women with peripartum cardiomyopathy disclosed the presence of viral genomes, this rate is not different from that of pregnant women without peripartum cardiomyopathy (Fett JD. Viral particles in endomyocardial biopsy tissue from peripartum cardiomyopathy patients [letter]. Am J Obstet Gynecol 2006;195:330–1.).[28] Another proposed etiology of peripartum cardiomyopathy is activation of the immune system by fetal microchimerism in which fetal stem cells or myocytes are embedded in the maternal heart and are recognized as foreign antigens.[4]

A plausible unifying hypothesis of the pathophysiology of peripartum cardiomyopathy has emerged from seminal observations made over the past few years. One of the most convincing associations leading to peripartum cardiomyopathy is that it is genetically predisposed. As previously discussed, this is evidenced epidemiologically by racial and geographic variations as well as by familial clustering. To buttress these findings, mutations in the *TTNC1* and *TTN* genes that encode cardiac myoprotein troponin C and titin have been identified in women with peripartum cardiomyopathy. Another important observation by Hilfiker-Kleiner and colleagues[29] showed that knockout mice that lacked the cardioprotective *STAT3* gene developed peripartum cardiomyopathy. These mice had increased production of the enzyme cathepsin D peptidase that cleaves the prodigiously secreted pregnancy hormone prolactin. As shown in Figure 1, this enzymatic action results in the formation of vasoinhibin–a 16-kDa peptide of prolactin that has vasculotoxic and proinflammatory properties.

In this scheme, vasoinhibin stimulates cardiac endothelium to express microRNA-146α that promotes myocardial endothelial cell apoptosis.[30] Vasoinhibin has been found to be elevated in women with peripartum cardiomyopathy and myocardial tissue from women with peripartum cardiomyopathy was found to have reduced *STAT3* expression with elevated levels of cathepsin D and vasoinhibin.[29] To add credence to this proposed mechanism, bromocriptine, which inhibits pituitary prolactin secretion, and thus lactation, prevents peripartum cardiomyopathy in *STAT3* knockout mice and, as subsequently discussed, and has also been reported to improve clinical outcomes in women with peripartum cardiomyopathy.[31,32] Together these findings indicate that genetic variants of cardiac muscle proteins play a role in the development of peripartum cardiomyopathy.[4,22]

The soluble vascular endothelial growth factor receptor–soluble fms-like tyrosine kinase-1 (sFlt-1)–is another important piece of the pathophysiology puzzle of peripartum cardiomyopathy. This antiangiogenic molecule triggers peripartum cardiomyopathy in susceptible mice that can be reversed with infusions of vascular endothelial growth factor and bromocriptine.[33] There is a well-known association between elevated sFlt-1 levels and preeclampsia, and, as discussed, the prevalence of preeclampsia is many times increased in women with peripartum cardiomyopathy compared with those without.[34,35] This association also may explain the disparate prevalence of multifetal pregnancy in women with peripartum cardiomyopathy, vis-à-vis concomitant hyperplacentosis and predisposition to preeclampsia. Interestingly and inexplicably, sFlt-1 serum levels are 10–15 times higher at 4–6 weeks postpartum in women who have peripartum cardiomyopathy compared with those who do not.[33]

Summary

The current theory regarding the pathophysiology of peripartum cardiomyopathy is that of a "two-hit hypothesis."[36] In this regard, peripartum cardiomyopathy affects genetically susceptible women who have one of several gene mutations to include *TTNC1, TTN*, and *STAT3*. Pregnancy at term is further characterized by prodigious secretion of prolactin by the maternal pituitary, and at the same time, the placenta secretes high levels of the antiangiogenic molecule sFlt-1. Although a number of putative triggering events have been hypothesized, the 16-kDa prolactin fragment–vasoinhibin–acts to cause myocardial damage with clinically apparent ventricular dysfunction. This is made worse by secretion of high levels of the vascular endothelial growth factor inhibitory molecule, sFlt-1,

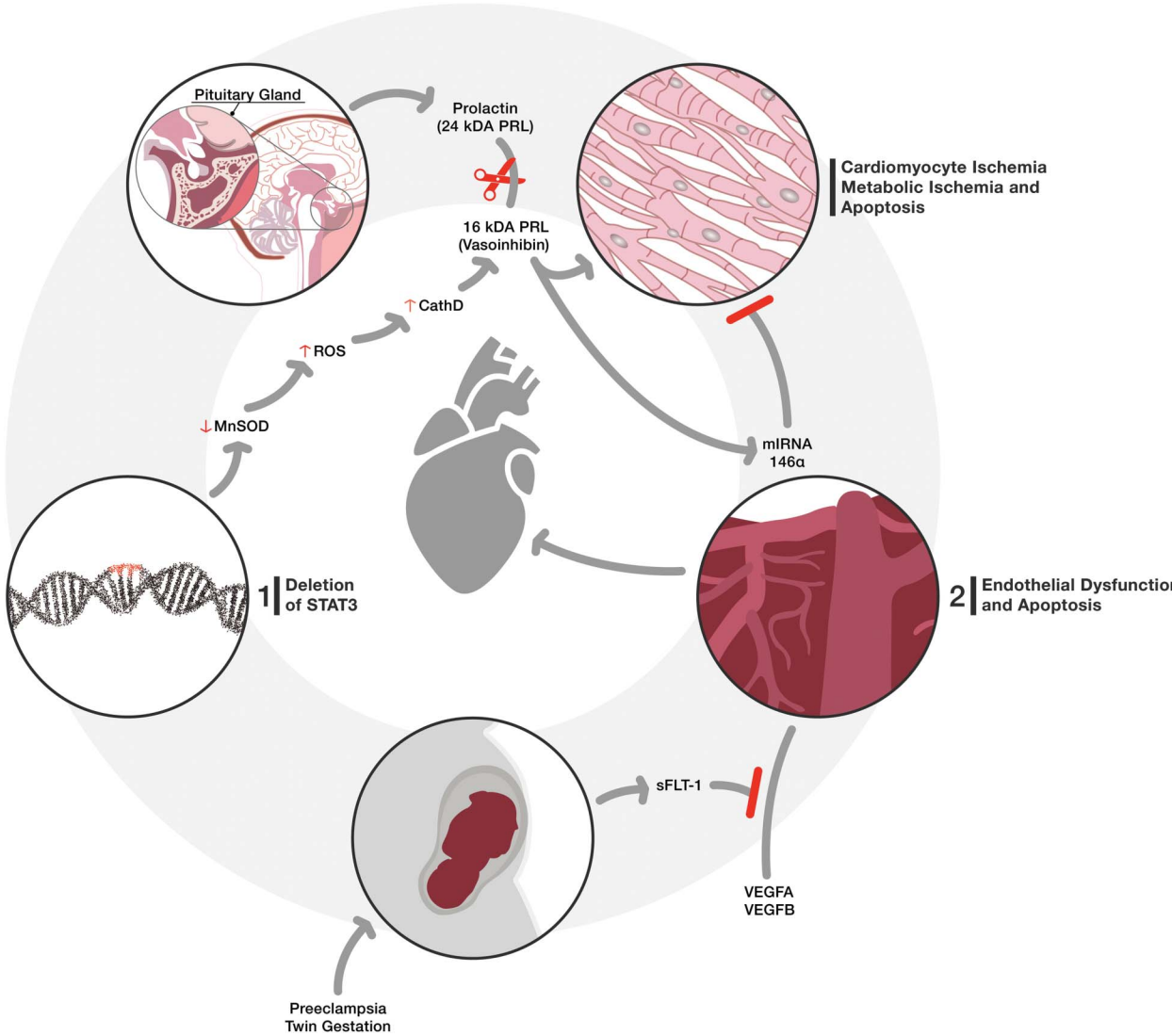

Fig. 1. Proposed pathogenesis of peripartum cardiomyopathy: 1) genetic predisposition caused by mutations of various genes (*STAT3, TTN, TTNC1*) that regulate cardiomyocyte function causes secretion of cathepsin D (CathD), which cleaves pituitary prolactin (PRL) to form a 16-kDa fragment, vasoinhibin; 2) vasoinhibin acts on blood vessels to trigger apoptosis as well as microRNA-146α resulting in cardiomyocyte ischemia, metabolic insufficiency, and apoptosis. Simultaneously, the placenta, especially with the preeclampsia syndrome, secretes soluble fms-like tyrosine kinase 1 (sFlt-1), which neutralizes vascular endothelial growth factors A and B (VEGFA and VEGFB, respectively) that are critical for vascular health. MnSOD, mitochondrial antioxidant manganese superoxide dismutase; ROS, reactive oxygen species. Data from Arany Z, Elkayam U. Peripartum cardiomyopathy. Circulation 2016;133:1397–409; *and* Arany Z. Understanding peripartum cardiomyopathy. Annu Rev Med 2018;69:165–6. Illustrations created by Ceara Byrne, MS. Used with permission.

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which is superabundant in women with preeclampsia, multifetal pregnancy, or both.

CLINICAL PRESENTATION

The woman with peripartum cardiomyopathy typically presents with symptoms of congestive heart failure in late pregnancy or in the early weeks of the puerperium.[1,23] Common symptoms are dyspnea on exertion, orthopnea, cough, fatigue, abdominal discomfort, and peripheral edema. Some women have chest pain and others report palpitations. Almost half will have peripartum hypertension and, commonly, preeclampsia.[27,32,35]

The most frequent clinical findings are attributed to congestive heart failure and its severity. Tachypnea, tachycardia, and rales and other evidence for

pulmonary edema predominate and there is usually increased jugular venous pressure and pitting edema of the lower extremities. In many women, tachycardia is accompanied by a gallop rhythm, but the heart rate may be too rapid for this to be appreciated. If chest pain is severe, the clinical picture may suggest a pulmonary embolism or myocardial infarction. Many affected women are overtly hypertensive at presentation, and there is frequent evidence for the preeclampsia syndrome. As shown in Figure 2, the chest radiograph discloses an increased cardiac silhouette with varying degrees of pulmonary congestion and edema.

Transthoracic echocardiography is diagnostic. The standard examination usually shows left ventricular dilation and systolic dysfunction, right ventricular and biatrial enlargement, mitral tricuspid regurgitation, and pulmonary hypertension.[22,37] In the European worldwide registry of 411 patients, right ventricular function was normal in half, mildly abnormal in approximately 35%, and severely abnormal in 10%.[38]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes common causes of pulmonary edema from both increased vascular permeability and cardiac failure. In pregnancy, the leading etiologies are hypertensive cardiomyopathy, superimposed preeclampsia, valvular disease, and sepsis. For example, severe preeclampsia with vigorous fluid replacement can cause pulmonary edema from a capillary–endothelial leak and decreased plasma oncotic pressure, and multifetal gestation and certain tocolytic agents (eg, terbutaline) increase this vulnerability. Sepsis syndrome worsens any underlying capillary leak from endothelial inflammation and can result in myocardial dysfunction from sepsis-induced cardiomyopathy. Other much less common causes of peripartum heart failure and pulmonary edema include pulmonary embolism, thyrotoxicosis, lupus erythematosus, and myocardial infarction. Thus, peripartum cardiomyopathy is a diagnosis of exclusion.

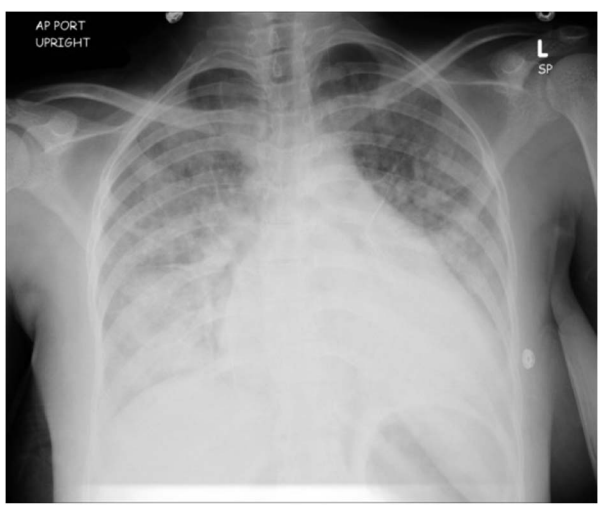

Fig. 2. Chest radiograph showing an enlarged heart and pulmonary edema in a woman with peripartum cardiomyopathy.

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CLINICAL INVESTIGATION

Although there are no diagnostic biomarkers for peripartum cardiomyopathy, measurement of natriuretic peptides have been used to assist in the diagnosis. B-type natriuretic peptide (BNP) and aminoterminal pro-BNP (NT pro-BNP) levels in the healthy pregnant woman are the same values as nonpregnant individuals.[39] A slight elevation in the BNP and NT pro-BNP has been seen within 48 hours postpartum period.[40] Additionally, BNP levels can be mildly elevated in patients with severe preeclampsia.[39] Although these levels are abnormally elevated in women with peripartum cardiomyopathy, there is no specific threshold for diagnosis.

Assessment of liver, kidney, and thyroid function is recommended along with evaluation for anemia and sepsis. Proteinuria should also be quantified. A summary of the complete evaluation recommendations are shown in Figure 3. The 12-lead electrocardiogram usually shows only sinus tachycardia with nonspecific changes.[22] Chest radiographs disclose cardiomegaly, usually with pulmonary congestion and pleural effusions (Fig. 2). Echocardiography remains the gold standard for confirmation of diagnosis and should be obtained as soon as possible. It typically demonstrates evidence of atrial and ventricular dilatation and reduced left ventricular systolic function.[41] Hibbard et al[37] proposed stringent criteria to diagnose peripartum cardiomyopathy and these are listed in Box 2. Of these, ejection fraction is most reproducible and widely used. Fractional shortening is the reduction in the length of the end-diastolic diameter of the ventricle that occurs in the end of systole. A caveat to these criteria is that left ventricular end-diastolic volume may be normal in peripartum cardiomyopathy.

The role of cardiac magnetic resonance imaging in investigation of peripartum cardiomyopathy is unclear at this time. Although there may be benefits to the use of cardiac magnetic resonance imaging in diagnosis and prognosis in women with peripartum cardiomyopathy, available data are limited.[42,43]

Although once recommended in the past, currently there is no role for routine endomyocardial

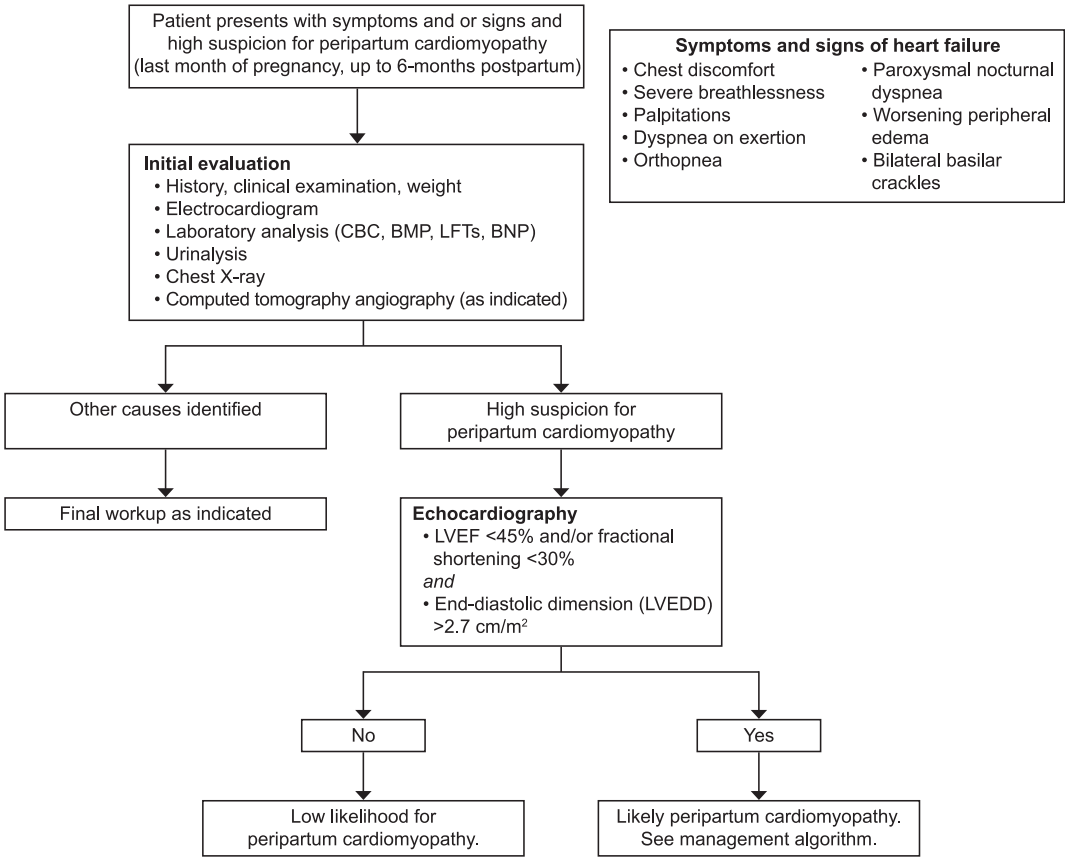

Fig. 3. Evaluation of the woman with suspected peripartum cardiomyopathy. CBC, complete blood count; BMP, basic metabolic panel; LFT, liver function test; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter.

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biopsy. An exception is that it may be indicated in the woman for whom there is consideration for heart transplantation.

Box 2. Criteria for Diagnosis of Peripartum Cardiomyopathy

- Heart failure within 1 month prior to delivery or 5 months postpartum
- Absence of other sources of heart failure
- Absence of heart disease prior to 1 month before delivery
- Echocardiography criteria showing left ventricular dysfunction:
  - Ejection fraction <45% AND/OR
  - Motion-mode fractional shortening <30%
  - Left ventricular end diastolic dimension >2.7 cm/m^2

Modified from Hibbard JU, Lindheimer M, Lang RM. A modified definition for peripartum cardiomyopathy and prognosis based on echocardiography. Obstet Gynecol 1999;94:311–6.

Determination of plasma microRNA-146a levels has been suggested to be a possible biomarker for both diagnosis and risk stratification of peripartum cardiomyopathy.[30] Specifically, microRNA-146a was reported to be elevated in the plasma and heart tissues of women with peripartum cardiomyopathy compared with levels in postpartum women without peripartum cardiomyopathy as well as nonpregnant women with idiopathic dilated cardiomyopathy. At this time, this biomarker is used for research only.

MANAGEMENT

An algorithm for management of peripartum cardiomyopathy is shown in Figure 4. Although the diagnosis of peripartum cardiomyopathy is most frequently made postpartum, for women diagnosed before delivery, timing of delivery will depend on several factors. These include gestational age, clinical condition, and proximity to a high-risk obstetrics center with experience in cardiovascular disease.[44] If symptoms can be

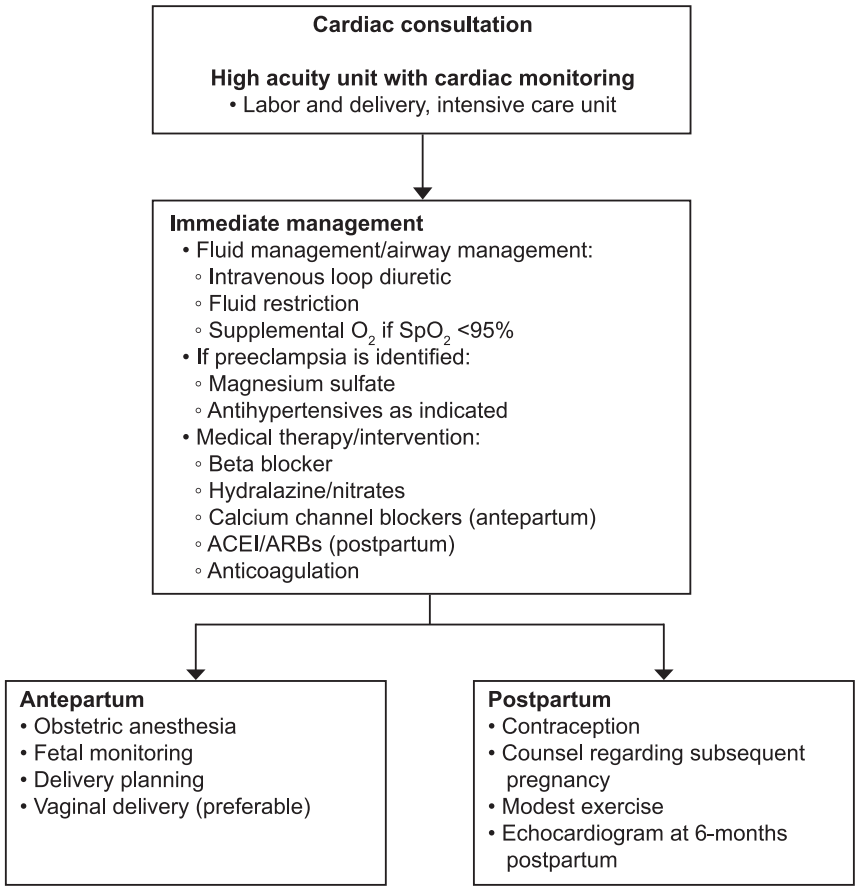

Fig. 4. Management of the woman with peripartum cardiomyopathy. SpO_2, peripheral capillary oxygen saturation; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

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managed with medical therapy, close monitoring is prudent, with pregnancy continuation to allow for fetal maturation. However, when peripartum cardiomyopathy occurs during pregnancy, it does so almost always in the last month; therefore, in most, cases there is little fetal benefit to continue pregnancy. A multidisciplinary team of obstetricians, cardiologists, maternal–fetal medicine specialists, and anesthesiologists should be involved in the decision-making process regarding timing and mode of delivery.

Vaginal delivery is preferable in a stable patient. Some recommend forceps- or vacuum-assisted delivery to decrease the risk of negative effects from the Valsalva maneuver.[44,45] Conversely, if there is evidence of severe maternal compromise or obstetric reasons are identified, cesarean delivery may be prudent.[46] Use of oxytocin follows the usual guidelines and does not require further dilution, and magnesium sulfate prophylaxis is commonly given as a result of concomitant preeclampsia. Thus, fluid status must be carefully monitored. Regardless of the route of delivery, the woman is placed in the lateral decubitus position to limit aortocaval compression. For some high-risk women–those with an extremely low ejection fraction or dangerous arrhythmias–continuous telemetry may be useful. Finally, some recommend invasive hemodynamic monitoring during labor and delivery.[44]

Analgesia and Anesthesia

As with any pregnant woman with serious heart disease, obstetric anesthesiologists are critical members of the team. For women with antepartum or intrapartum peripartum cardiomyopathy, considerations are analgesia for labor and vaginal and cesarean delivery. Labor epidural analgesia is ideal and is induced slowly in the event of a fixed cardiac output.[15] Careful attention is given to fluid administration and especially blood replacement. In some women, spinal–epidural analgesia is required for cesarean delivery, and general anesthesia is occasionally indicated.[47] Although there is not a consensus regarding invasive monitoring as noted previously, pulmonary artery catheterization is seldom used today. In some cases, transesophageal echocardiography may be used.[48]

Medical Therapy

The standard management of peripartum cardiomyopathy is based on the treatment of systolic heart failure.[22] Treatment is focused on controlling symptoms, repressing neurohormonal responses, and preventing long-term sequelae such as thromboembolic disease and arrhythmias. Management of symptoms can usually be achieved through optimizing fluid status and improving pulmonary function. Aggressive diuresis is instituted along with electrolyte monitoring. Loop diuretics such as furosemide exert their action by reducing the intravascular volume and thus preload.[44] Oxygen therapy can be useful for hypoxemic patients, although its utility is of uncertain benefit in other patients with cardiac disease.[49]

Angiotensin-converting enzymes inhibitors and angiotensin-receptor blockers function to decrease afterload and are one of the cornerstone treatment options for peripartum cardiomyopathy in postpartum women. Because of their teratogenic effects, they are avoided during pregnancy and alternatives such as hydralazine and nitrates may be used for their vasodilatory effects. Calcium channel blockers are also safe in pregnancy and are routinely used for hypertension. In the PRAISE Heart Failure Trial, amlodipine was shown to decrease the plasma level of interleukin-6, which has been reported to be high with peripartum cardiomyopathy.[50,51] Finally, β-blocking agents have been shown to reduce mortality. At this time, some recommend continuing angiotensin-converting enzymes inhibitors and β-blockers for at least 1 year after resolution of symptoms and improvement in left ventricular function.[52]

Treatment with digoxin is currently debated.[22] Its primary utility may be in women with symptoms that are refractory to standard therapy with angiotensin-converting enzymes inhibitors, β-blockers, and diuretics. Digoxin can improve cardiac myocontractility through inhibition of the sodium–potassium adenosine triphosphate pump, and it inhibits sympathetic outflow, which will improve cardiac output.

Thromboembolism Prophylaxis

Peripartum cardiomyopathy is associated with higher rates of thromboembolism than other forms of cardiomyopathy.[22,23] This is predisposed from heart chamber dilatation; the risk is increased even further if there is atrial fibrillation. In a nationwide inpatient database of women with peripartum cardiomyopathy, thromboembolism was the most serious complication with an incidence of 6.6%.[26] In another study, Goland et al[53] reviewed 182 women with peripartum cardiomyopathy and reported that 2.2% experienced a thromboembolism. Given the high risk of thromboembolism, it seems prudent to provide anticoagulation in prophylactic doses during pregnancy and the immediate postpartum period.[22]

Arrhythmias

Sudden death is a frequent cause of mortality with peripartum cardiomyopathy, and this is presumed to be from ventricular arrhythmias in most cases. In an observational study of 182 patients, 38% of mortality was attributed to sudden death.[53] Although studies have described the use of implantable cardioverter–defibrillators, neither their permanent use nor wearable devices are currently recommended prophylactically.[22]

Ventricular Assist Devices and Cardiac Transplantation

For patients with severe depression of ventricular dysfunction, intra-aortic balloon pumps, ventricular assist devices, and even extracorporeal membrane oxygenation have been used pending recovery of function or as a bridge to cardiac transplantation. Indeed, 5% of cardiac transplants in women in the United States are for peripartum cardiomyopathy.[54]

Prolactin Inhibition

Because of the central role that prolactin putatively has in the pathogenesis of peripartum cardiomyopathy, some empirically recommend against breastfeeding.[22,55] For this reason, the prolactin-inhibiting agent bromocriptine has been given to women with peripartum cardiomyopathy in an attempt to mitigate ventricular damage.[56,57] A small randomized trial of 20 African women showed significant improvement in ventricular function in those given bromocriptine. In a larger observational German registry, the use of bromocriptine was associated with improved ventricular function compared with no bromocriptine therapy. In a recent multicenter randomized trial, Hilfiker-Kleiner et al[58] compared 1-week and 6-week bromocriptine treatment both combined with standard heart failure therapy. Women given either of two bromocriptine regimens had a high rate of full left ventricular recovery as well as decreased morbidity and mortality when compared with peripartum cardiomyopathy cohorts from studies in which bromocriptine was not given. Although these investigators concluded that their findings further supported a potential benefit of bromocriptine for women with peripartum cardiomyopathy, it is not currently U.S.

Food and Drug Administration–approved for this purpose.

Breastfeeding and Contraception

Clinical evidence for salutary effects of curtailment of breastfeeding is lacking. Because of the likely role of prolactin in peripartum cardiomyopathy, some have recommended against breastfeeding. Regarding contraception, the U.S. Medical Eligibility Criteria for Contraceptive Use have classified either as one or two –suitable–copper or levonorgestrel intrauterine devices, etonogestrel implants, depot medroxyprogesterone acetate, and progestin-only pills.[59] The guidelines advise against the use of combined estrogen–progestin oral contraceptives given the increased risk of fluid retention and induction of cardiac arrhythmias.

FOLLOW-UP AND SUBSEQUENT PREGNANCY

Repeat echocardiography is routinely recommended at least 6 months after pregnancy to evaluate ventricular function. Once there is recovery, annual echocardiography is performed.[54] Preconceptional counseling with a maternal–fetal medicine specialist and a cardiologist is recommended if further pregnancies are desired. An echocardiogram should be obtained before pregnancy to better counsel the woman regarding risks of morbidity and mortality of another pregnancy. Baseline measurement of BNP levels prepregnancy is recommended as comparator levels to be followed serially through pregnancy.

The risk for recurrence of peripartum cardiomyopathy in subsequent pregnancy is based on retrospective data. Elkayam et al[60] compared women who had subsequently regained normal left ventricular function with those who had persistently decreased function. The latter had a higher rate of heart failure compared with those women with normal function–44% compared with 21%–as well as a higher mortality rate–19% compared with none, respectively. Importantly, all pregnancies were associated with a reduction in left ventricular ejection fraction. In a recent study from the Mayo Clinic, 25 women with peripartum cardiomyopathy, of whom 24 had recovered ventricular function, were followed through 33 live birth pregnancies.[61] Although most of these women had a decline in left ventricular function, only 21% had recurrent peripartum cardiomyopathy. Importantly, however, all of the women recovered ventricular function after pregnancy. Of interest, there was a high rate of breastfeeding in these women after their subsequent deliveries.

PROGNOSIS

The ventricular function recovery and mortality rate with peripartum cardiomyopathy vary by epidemiologic and geographic patient populations. In an indigent U.S. population, the ventricular function recovery rate was 65% with the remaining 35% having an ejection fraction less than 45%.[62] This is similar to data from the multicenter Investigations of Pregnancy Associated Cardiomyopathy in which 72% of 100 women with peripartum cardiomyopathy had an ejection fraction greater than 50% by 12 months.[63] These data emphasize the need for serial surveillance and echocardiography. There is evidence that black women have an overall worse prognosis vis-a-vis severity of peripartum cardiomyopathy and long-term recovery.[64] This is borne out by recovery rates reported from Haiti, Turkey, and South Africa, which were only 21–43% (Fett JD. Long-term maternal outcomes in patients with peripartum cardiomyopathy (PPCM) [letter]. Am J Obstet Gynecol 2009;201:e9).[65,66]

Mortality rates likewise vary according to geographic locale and the time period of the study. From the worldwide registry in Europe that described 411 patients with peripartum cardiomyopathy, the overall death rates within 1 month of diagnosis were approximately 3%.[39] Similarly, there were four deaths in the Investigations of Pregnancy Associated Cardiomyopathy study, which included 100 women from multiple U.S. medical centers who were followed for 12 months.[63] In a population-based study from North Carolina in which 85 women were followed for 7 years, there were 14 deaths (16%) caused by peripartum cardiomyopathy or related problems.[67] By contrast, the mortality rate in South Africa is 28–40%, from Haiti it is 15–30%, and in Turkey, 30% (Fett JD. Am J Obstet Gynecol 2009;201:e9).[65]

SUMMARY

Although there have been significant advancements in understanding peripartum cardiomyopathy as well as development of improved management strategies, this uncommon enigmatic disease continues to be a cause of significant pregnancy-associated morbidity and mortality. Careful diagnosis of peripartum cardiomyopathy is paramount in understanding the epidemiologic vicissitudes of the disease and to improve appropriate treatment. Currently, its management is limited to nonspecific heart failure treatment, given there are no proven disease-focused therapies. In light of the increasing incidence of peripartum cardiomyopathy, further research is needed to develop targeted therapies.

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