Favorable course of peripartum cardiomyopathy (RCD code: VII-III-5C)

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Abstract

Peripartum cardiomyopathy (PPCM) is defined as an idiopathic cardiomyopathy, presenting with heart failure (HF) secondary to left ventricular systolic dysfunction (LVSD) at the end of pregnancy or in the early months after delivery. Importantly, there should be no other identifiable cause of HF. The pathophysiology of PPCM is not fully understood and is probably multifactional. The data on the PPCM prognosis are sparse. Though initial reports suggested that mortality in PPCM vary geographically. We present a case of a nulliparous 25-year-old Caucasian woman, who gradually developed dyspnea on exertion and fatigue 2 months after successful vaginal twin delivery. She did not have any typical risk factors for cardiovascular diseases, her family history was unremarkable, and the whole pregnancy period was uneventful. After initiation of anti-HF therapy her clinical status gradually improved and she was discharged home with only mild symptoms and improved LV systolic function. JRCD 2015; 2 (3): 85–88

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Background

Peripartum cardiomyopathy (PPCM) has been variably defined over the years. The most recent definition, issued in 2010 by the Heart Failure Association of the European Society of Cardiology, states that it is an idiopathic cardiomyopathy, presenting with heart failure (HF) secondary to left ventricular (LV) systolic dysfunction at the end of pregnancy or in the early months after delivery. Importantly, there should be no other identifiable cause of HF. The main difference between the European and American perspectives is that the European experts no longer use the specific time frames of 1 month prior to and 5 months after delivery when PPCM can be diagnosed [1].

Case description

Previously fit and well, a nulliparous 25-year-old Caucasian woman, gradually developed dyspnea on exertion and fatigue 2 months after successful vaginal twin delivery. The patient did not have any typical risk factors for cardiovascular diseases, her family history was unremarkable, and the whole pregnancy period was uneventful. Eventually, she was urgently admitted because of resting dyspnea and massive peripheral edemas. At presentation, she was clearly decompensated with a heart rate of 130 beats/min, arterial blood pressure of 90/60 mm Hg, oxygen saturation of 90% (on air), respiratory rate of 20 per minute; she was classified as New York Heart Association (NYHA) class IV. Physical examination revealed lung congestion (Killip class 2/3), massive lower-limb edema up to the thighs, raised jugular venous pressure, and possible ascites. On an electrocardiogram, she was in sinus tachycardia with right-axis deviation and with signs of left atrial enlargement. Echocardiography revealed dilatation of the LV (LV end-diastolic diameter, 71 mm), severe global contractility impairment with the ejection fraction of 8% calculated by the Simpson’s method, with accompanying severe pulmonary and tricuspid regurgitation but without the features of pulmonary hypertension (right ventricular systolic pressure of 30 mm Hg and pulmonary acceleration time of 138 ms) (fig. 1–3). Laboratory test results showed slight anemia (hemoglobin levels, 13.3 g/dL; hematocrit, 38.8%), significantly increased levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP, 6910 pg/mL), and no signs of systemic infec-
tion (white blood count, 7.56; high-sensitive C-reactive protein, 1.4 mg/L; procalcitonin, 0.06 ng/mL). Because the patient’s clinical status deteriorated rapidly, pharmacologic circulatory support with catecholamines (dopamine and dobutamine) and small doses of intravenous diuretics were started. After a few days, her hemodynamic status greatly improved and catecholamines were safely withdrawn. Subsequently, a low dose of prolactin inhibitor (bromocriptine) and β-blocker (carvedilol, 3.125 mg twice daily) were introduced. Unfortunately, the combination of a β-blocker and angiotensin-converting-enzyme inhibitor (ACEI) resulted in pronounced hypotension; therefore, we continued only with a β-blocker. After a week of progressive clinical improvement, echocardiography showed a significant increase in the LV ejection fraction (LVEF, about 20%), which was associated with a decrease in NT-proBNP levels (1833 pg/mL). After another week, the patient was able to walk a distance of 100 meters and climb one flight of stairs and was discharged home. At the follow-up visits 2 and 4 weeks later, we observed clinical and echocardiographic improvement. At present, she is in NYHA class II with significant reverse remodeling (LV end-diastolic diameter, 58 mm; LV end-systolic diameter, 48 mm). At present, she is no longer on bromocriptine and we could introduce an ACEI (ramipril, 2.5 mg twice daily).

**Discussion**

**Epidemiology**

The precise epidemiology of PPCM in the general population is unknown [2–4]. A few studies, performed in various geographic locations, particularly in the United States, Haiti, South Africa, and Nigeria, provide conflicting data. The incidence of PPCM is about 1:2500–4000 pregnancies in the United States, 1:1000 in South Africa, 1:300 in Haiti, and it is unprecedentedly high in Nigeria – 1:100. Unfortunately, there is lack of epidemiological studies from the European region.

The course of the disease is largely unpredictable with roughly two-thirds of the cases showing spontaneous improvement, while the remaining one-third of the cases showing severe or even end-stage HF.
Pathophysiology

The pathophysiology of PPCM is not fully understood and is probably multifactorial. Apart from hormonal imbalance, other potential mechanisms may be implicated in the disease pathology, such as myocardial inflammation, abnormal immune response to fetal antigen, and hemodynamic factors. Moreover, familiar and geographical clustering of PPCM suggests that the genetic background and environmental factors may be significant contributors.

Although not completely understood, new data are emerging on the possible role of oxidative stress, nursing-hormone prolactin, and the prolactin-cleaving protease, cathepsin D, in the pathology of PPCM. In the late pregnancy and early postpartum, cellular oxidation is particularly high and activates cathepsin D in cardiomyocytes, which eventually transforms prolactin into angiotastic and proapoptotic subfragments. In an experimental mouse model of PPCM, the 16 kDa fragment of prolactin was responsible for various detrimental effects on the cardiovascular system, such as endothelial cell apoptosis, vasoconstriction, and impairment of cardiomyocytes function and metabolism. Although not definitively confirmed in humans, it seems that the damaging complex of oxidative stress–cathepsin D–16kDa prolactin can be broken by the suppression of prolactin production by dopamine D2 receptor agonist, bromocriptine, which favorably alters the course of PPCM.

A number of risk factors have been associated with increased risk of PPCM, including age over 30 years, multiparity, African descent, pregnancy with multiple fetuses, a history of preeclampsia, eclampsia, or postpartum hypertension, maternal cocaine abuse, more than 4 weeks of oral tocolytic therapy with β-adrenergic agonists [1].

Clinical manifestations

Most of the symptoms are related to systolic dysfunction of the LV and are similar to those observed in other forms of systolic HF. Symptoms range from mild to very severe. Severe symptoms may result in death. PPCM is characterized by dyspnea on exertion in mild cases or dyspnea at rest in more severe stages, orthopnea, lower-limb edema, and persistent cough. Additional symptoms include abdominal discomfort, which is secondary to hepatic and gastrointestinal congestion, as well as palpitations, and dizziness. Patients and clinicians often attribute the symptoms either to gravidity or general weakness as well as associated anemia, which often results in misdiagnosis. Therefore, the most frequent initial presentation is associated with the symptoms of NYHA class III or IV [1,5]. Importantly, delays in diagnosis and treatment are associated with increased mortality. In order to promptly make the diagnosis of PPCM, the Working Group on peripartum cardiomyopathy of the HF Association developed a simple algorithm (Figure 4).

Diagnosis of peripartum cardiomyopathy

PPCM is a diagnosis of exclusion, where both cardiac and noncardiac symptoms should be carefully evaluated. In patients who are clinically suspected of having PPCM, electrocardiogram, echocardiography, and the measurement of brain natriuretic peptide levels (BNP or NT-proBNP) should always be performed [1].

Electrocardiogram

The most common findings on electrocardiogram include sinus tachycardia or, rarely, atrial fibrillation, signs of LV hypertrophy, unspecific ST-T-wave abnormalities, and, occasionally, Q waves in anterior precordial leads, PR interval, and the QRS complex may be prolonged [1].

Echocardiography

Echocardiography is the most important and widely used diagnostic method to confirm the diagnosis and to monitor the effectiveness of ongoing treatment. The examination typically reveals LV dilatation with or without hypertrophy and a global reduction of contractility. The cut-off values of LV dilatation and systolic dysfunction to diagnose PPCM have not been precisely defined. In daily practice, LV end-systolic dimension exceeding 27 mm/m² and the LVEF of less than 45% is considered as indicative of PPCM. Other abnormalities such as left atrial enlargement, secondary mitral and tricuspid regurgitation, or small pericardial effusion are frequently observed in PPCM. Apart from the initial examination, echocardiogram should be repeated before discharge, at 6 weeks, 6 months, and once a year to evaluate cardiac recovery or disease relapse. Predictors of poor LV function recovery are the baseline LVEF of less than 30% and LV end-diastolic diameter exceeding 60 mm [6,7].

Brain natriuretic peptides

As in virtually any severe form of HF, the levels of BNPs are significantly elevated during the course of PPCM as a result of systolic dysfunction and elevated end-diastolic pressure [1].

Chest radiography

Although chest radiography has limited diagnostic accuracy, it is frequently performed to assess the status of pulmonary congestion but, even more importantly, to search for other causes of breathlessness.

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging (MRI) is definitively less often used than echocardiography but it provides a more accurate measurement of chamber volumes, wall thickness, and regional and global systolic functions, and has higher sensitivity for the detection of thrombus. Moreover, a few studies showed that the presence of late gadolinium enhancement was associated with poor recovery of cardiac function. Finally, cardiac MRI has better diagnostic accuracy for myocarditis, which should also be considered in the diagnostic pathway. According to the European Society of Radiology, gadolinium contrast should be avoided until delivery but breast-feeding does not have to be interrupted [8].

It is important to distinguish PPCM from other preexisting cardiomyopathies, such as dilated cardiomyopathy unmasked by pregnancy, HIV/AIDS cardiomyopathy, and other prior cardiac disorders including valvular heart disease, hypertensive heart disease, unrecognized congenital heart disease, pregnancy-associated myocardial infarction, or pulmonary embolus.
Management

The principles of treatment of patients with PPCM, either in acute or chronic state of HF is not very different from the other types of HF.

Acute heart failure

In the acute setting, there are three goals, namely, optimization of hemodynamics, relief of symptoms, and initiation of chronic therapies approved for HF. This is usually achieved by appropriate oxygen therapy, intravenous diuretics, and, depending on hemodynamic status (hyper- or hypotensive), by vasodilators (e.g., nitroglycerin) or inotropic agents. In rare cases, more advanced mechanical circulatory support may be needed to stabilize the patient until recovery or as a bridge to heart transplantation.

Stable heart failure

Treatment depends on whether the patient is still pregnant or in the postpartum period because some of the drugs may have a negative effect on the fetus. It is generally believed that the treatment of stable HF after delivery should not be different from the current HF guidelines of the European Society of Cardiology [9]. In case of ongoing pregnancy, ACEIs and angiotensin receptor blockers (ARB) are contraindicated because of serious renal and fetal toxicity [10,11]. β-blockers are generally safe during pregnancy; however, caution is advised. As a rule, β₁-selective antagonists are preferred over β₂ as β-blockers are generally safe during pregnancy; however, caution is advised. Aldosterone antagonists, both spironolactone and eplerenon, should be avoided during pregnancy because of the unknown interactions with hormonal pathways. On the other hand, less frequently used hydralazine and long-acting nitrates are valuable replacements for ACEIs and ARBs [13]. Finally, antithrombotic therapy should be considered in patients with seriously depressed LVEF, especially in the setting of atrial fibrillation. Vitamin K antagonists should rather be avoided owing to potential fetotoxicity as well as difficulties in the management of patients on this therapy. Generally safe and much easier to manage are unfractionated or low-molecular-weight heparins. Implantable cardioverter-defibrillators and cardiac resynchronization therapy devices, which have an important and proven role in the management of systolic HF, are occasionally implanted in women with persistent severe symptoms and lack of LV function recovery. However, the final decision of whether to implant an ICD or not is usually difficult and a natural course of PPCM (which is favorable in many patients) should also be considered in addition to numerous other factors.

Novel therapies

The rationale behind the treatment of PPCM with bromocriptine comes from an experimental study on mice, in which PPCM was prevented with this agent via prolactin blockade. In a randomized open-label study of newly-diagnosed PPCM in South African women, an addition of 2.5 mg bromocriptine twice daily for 8 weeks to standard HF treatment resulted in a significant improvement of HF symptoms and LVEF. Although bromocriptine seems to be a promising “tailored” adjunctive therapy of PPCM, its safety and efficacy needs to be verified in larger randomized trials before it can be widely recommended in the guidelines [1].

Immunosuppressive agents have been anecdotally used in women with PPCM and biopsy-proven myocarditis with good results. However, its routine use is currently not recommended. Similarly, intravenous immunoglobulin has also been tried in concurrent PPCM and myocarditis but is not a standard of care.

Prognosis

The data on the PPCM prognosis are sparse. Although initial reports suggested that mortality in PPCM vary geographically, the more recent reports suggest similar rates of survival in women from the United States, Haiti, and South Africa. Unfortunately, there are no mortality studies in European women. The largest series of 123 women with PPCM showed a mortality rate of approximately 10% at follow-up of 2 years. A slightly worse outcome was observed in women from South Africa with the mortality of 10% and 28% in 6-month and 2-year follow-up, respectively. The mode of death is typically progressive pump failure, sudden cardiac arrest, or thromboembolic events. The negative prognostic factors are as follows: worse NYHA class, Blacks, and multiparity. Fortunately, the functional status and cardiac function of the majority of patients improve with treatment, and over 50% of the patients experience complete recovery of heart function (LVEF of 55% or greater). Although the risk of PPCM relapse in subsequent pregnancies is not completely defined, it is generally believed that it is significantly increased compared with women without prior PPCM. Women who had not fully recovered form PPCM, have a particularly high risk of disease recurrence or exaggeration of symptoms. Though it is not formally supported by the guidelines and it is difficult to give individual counseling, women with a history of PPCM who have persistent LV dysfunction should be best advised to avoid pregnancy owing to the high risk of HF progression and death.

References