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Peripartum cardiomyopathy (a literature review)

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ABSTRACT

Heart failure (HF) is a serious and growing public health concern, which has many causes. Pregnancy is a critical condition with significant hemodynamic and immunologic changes. Peripartum cardiomyopathy (PPCM) is a disease of unknown cause in which left ventricular (LV) dysfunction occurs during the last trimester of pregnancy or the early puerperium. PPCM is known to be the most common cardiovascular cause of severe complications in pregnancy. Risk factors for peripartum cardiomyopathy include advanced maternal age, twin pregnancy, smoking, pregnancy-related hypertension and preeclampsia, multiparity, African descent, and long-term tocolysis. Oxidative stress and some inflammatory markers have been diagnosed in PPCM pathophysiology. Recent observations have suggested that bromocriptine might favor recovery of LV systolic function in patients with PPCM. Patients developed peripartum cardiomiopathy treated with bromocriptine showed significantly improved LV ejection fraction and heart failure symptoms. This article tries to have a short review on this clinical scenario.

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Introduction

Heart failure (HF) is a serious and growing public health concern, which has many causes and clinical scenarios and occurs in different patients. HF, which is defined as impaired organ perfusion and/or high filling pressure, involves many organs. Pregnancy is a critical period in a woman's life in which the heart and other organs encounter significant hemodynamic and immunologic changes that in certain cases can become

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problematic. PPCM is a disease of unknown cause in which left ventricular (LV) dysfunction occurs during the last trimester of pregnancy or the early puerperium, reported in 1:1300 to 1:4000 of live births (1). It is important for cardiologists and gynecologists to have enough knowledge, in this regard, in order to timely diagnose and manage such patients. In light of the above-mentioned points, the authors have compiled this review on PPCM with the aim of providing physicians with a succinct and useful guide on this clinical scenario.

Pathophysiology

PPCM is known to be the most common cardiovascular cause of severe complications in pregnancy (1,2). Risk factors for peripartum cardiomyopathy include advanced maternal age, twin pregnancy, smoking, pregnancy-related hypertension and preeclampsia, multiparity, African descent, and long-term tocolysis (1,2). Chemotherapy emerges as a risk factor for the later development of PPCM. Preeclampsia is a risk factor for cardiovascular disorders later in life. Most theories have focused on hemodynamic and immunologic causes.

Oxidative stress, low selenium levels and viral infections have contributed as possible causes. Recent data have suggested that uncontrolled oxidative stress leads to activation of the prolactin cleaving enzyme cathepsin D that increases in cleaved 16Kd prolactin, which has apoptotic and angiogenic roles that adversely affect cardiomyocytes and the endothelium and lead to cardiomyopathies (3).

Levels of prolactin in urine correlate with disease severity in preeclampsia patients. MIR-146a levels are increased and ErbB4 levels are reduced in the left ventricular tissue of PPCM patients. Investigation on a large cohort of PPCM patients demonstrated that this condition is associated with a pro-inflammatory response, as evidenced by elevated plasma levels of tumor necrosis factor, Fas-Apo-1, interleukin-6, and C-reactive protein (CRP) (3,4). More recently, Foster et al documented a close correlation between NT-proBNP; a marker of ventricular wall stress and heart failure, prolactin, and markers of oxidative stress (oxidized low-density lipoprotein) and inflammation (interferon), whichis supporting the detrimental role of the oxidative stress–prolactin axis.

CRP is usually normal or mildly elevated and oxidized LDL, which is a marker of oxidative stress, is increased incrementally, while INF, which is a marker of inflammation, decreased (5).

Walenta et al. suggested that certain micro-particles could be quantified in the serum as markers for the diagnosis and evaluation of treatment effects in PPCM. It is now well established that microparticles (MPs), released from cellular membranes during cell activation/apoptosis, may play a pivotal role as bioactive molecules.

Endothelial metaloproteinases (EMP) could directly demonstrate endothelial damage in PPCM. Furthermore, platelet-derived metaloproteinases (PMPs), monocyte-derived (MMPs) and leukocyte-derived MPs (LMPs) can indicate the subsequent detrimental events like clot formation and inflammatory activation (5). In previous studies, MPs have been suggested to be a sign of severity in preeclampsia and MPs gained from women with preeclampsia elicit an intense vascular wall inflammation (6,7).

Clinical Findings

Symptoms and signs are often typical for heart failure but, due to the special physiological situation of pregnancy and postpartum, a broad spectrum of symptoms is reported in PPCM patients. PPCM should be suspected in all women with a delayed

return to the pre pregnancy state.

Patients complain of dyspnea on exertion which can progress to ordinary activities (NYHA, New York Heart association classification III or IV) or orthopnea and PND (paroxysmal nocturnal dyspnea). Some patients have positional and pitting edema after delivery while 19% happen in last months of pregnancy and some present with ventricular arrhythmias or abdominal discomfort (1). Chest pain is not common. Being pale, elevated JVP and systolic murmur in apex or left sternal border can be found in physical examination. Frequently the patients present with acute heart failure. Complex ventricular arrhythmias and sudden cardiac arrest are also described (8).

The clinical course is highly variable from spontaneous recovery of ventricular function to rapid progression, and end stage HF.

Diagnosis

An early diagnosis of PPCM is essential for the initiation of lifesaving treatments like inhibition of prolactin (PRL) with bromocriptine, which its effect is also mirrored by the MP profile. Diagnosis of PPCM is often missed at early stages of this life-threatening disease Walenta et al speculated that a typical MP profile could be of diagnostic importance in PPCM. Microparticle expression profiles differentiated PPCM patients from cardiomyopathies of cardiovascular causes such as ischemic cardiomyopathy (ICM) (4).

Therapeutic intervention using bromocriptine decreased the EMP levels in these patients. A marker enabling early detection of PPCM and distinguishing it from other changes of pregnancy like fluid overload with peripheral edema, shortness of breath and alteration of end-diastolic volumes is needed for early diagnosis and treatment of this devastating condition. Endothelial and platelet MP changes specifically indicate PPCM and might facilitate the diagnosis of this life-threatening condition; thereby they clearly distinguish it from heart failure of other etiologies and vascular diseases in the absence of heart failure or pregnancy (4).

In some cases, not all diagnostic criteria may be strictly fulfilled. Echocardiography is the preferred method to assess LV function. Genetically transmitted DCM may manifest in the same time interval and is not distinguishable from PPCM (8).

Echocardiography can be helpful in the diagnosis, we can see LV systolic and diastolic dysfunction in a woman with dyspnea or low output signs in late pregnancy or early post-delivery, but echocardiography cannot be diagnostic. Usually LV is not severe enlarged and spherical and myocardial thickness is preserved but this is not the rule and there is no documented data in this regard.

Management and Prognosis

PPCM is associated with high mortality and morbidity. Management of patients with peripartum cardiomyopathy (PPCM) is still a major clinical problem, as only half of them or slightly more show complete recovery of left ventricular (LV) function despite conventional evidence-based treatments for heart failure (2).

In the German PPCM registry, 10% of patients with a positive family history of DCM did not respond to medical treatment. Genetic analysis and counseling are recommended in these patients. In addition, it should be considered that pregnancy might damask familial cardiomyopathies (3).

The prognosis of peripartum cardiomyopathy is related to the recovery of ventricular function. Significant improvement in myocardial function is seen in 30% to 50% of patients in the first 6 months after presentation, and nearly 50% of LV dysfunction persists despite conventional medical treatment (1,2). For

those patients who do not recover to normal or near-normal function, the prognosis is similar to other forms of DCM with a 50% mortality rate at 6 years. The development of symptoms>4 weeks postpartum may be a manifestation of milder forms of this disease.

Subsequent pregnancy in women with a history of PPCM may be associated with a further decrease in LV function and can result in clinical deterioration, including death. There is an increased risk of venous thromboembolism. Therefore, anticoagulation is recommended, especially if ventricular dysfunction is persistent (1).

A subsequent pregnancy carries a recurrence risk for PPCM of 30-50%. When the EF has not normalized, a subsequent pregnancy should be discouraged. Even if the EF is normalized, there is still a need for counseling because of the risk of recurrence with a new pregnancy (8).

Treatment

Heart failure should be treated according to guidelines on acute and chronic heart failure (1,8). During pregnancy, ACE inhibitors, ARBs, and renin inhibitors are contraindicated because of fetotoxicity. When ACE inhibitors are needed during breastfeeding, captopril, or enalapril should be preferred.

Hydralazine and nitrates can be used instead of ACE inhibitors/ARBs for afterload reduction. Dopamine and levosimendan can be used if inotropic drugs are needed. B-Blocker treatment is indicated for all patients with heart failure, if tolerated. B1-Selective drugs (i.e. metoprolol) should be preferred. Atenolol should not be used.

Newborns should be supervised for 24-48 h after delivery to exclude hypoglycaemia, bradycardia, and respiratory depression. Diuretics should only be used if pulmonary congestion is present since they may decrease blood flow over the placenta. Furosemide and hydrochlorothiazide are most frequently used. Aldosterone antagonists should be avoided. Spironolactone can be associated with antiandrogenic effects in the first trimester (8).

Recent observations suggest that bromocriptine might favor recovery of LV systolic function in patients with PPCM. It has been hypothesized that addition of bromocriptine or other prolactin release inhibitors to standard therapy may be effective in favoring both clinical status and LV systolic and diastolic functions (9).

The rationale for the use of bromocriptine in PPCM is based on the hypothesis that increased oxidative stress in the postpartum heart may play a key role in the genesis of PPCM by enhancing the cathepsin D-mediated cleavage of prolactin into its 16-kDa subform, which has angiostatic and proapoptotic properties, promotes vasoconstriction, inhibits endothelial cell proliferation and migration, and favors myocardial micro-vascular injury (9).

Several case reports have also described seemingly beneficial effects of the addition of bromocriptine to standard heart failure therapy in patients with acute PPCM (10).

Bromocriptine may also affect metabolic parameters. Sliwa et al observed that PPCM patients display increased oxidized low-density lipoprotein serum levels compared to healthy postpartum women, suggesting impaired antioxidative defense mechanisms and potential metabolic perturbations (9).

In turn, Wexler and McMurrey reported that, experimentally, bromocriptine treatment reduced triglyceride, free fatty acid, total cholesterol, and glucose levels in isoproterenol-induced heart failure (10).

Whether such parameters play a role in the pathophysiology of PPCM is currently under investigation on experimental models. Preliminary data showed that bromocriptine treatment increased Akt activation and upregulated Bcl-2 expression in the heart of postpartum mice, suggesting

that bromocriptine may indeed have direct cardioprotective effects.

Sliwa and colleagues have evaluated the bromocriptine effect on PPCM patients in a randomized trial and concluded that the addition of bromocriptine to standard heart failure therapy improved left ventricular ejection fraction and was a composite clinical outcome in women with acute severe PPCM. However, the number of patients studied was small and the results could not be considered as final. Larger-scale multicenter and blinded studies are in progress to test this strategy more robustly (11).

Although these preliminary results suggesting beneficial effects of bromocriptine treatment in patients with acute PPCM, appear promising, concerns have been raised regarding the risk of thrombotic complications, including cerebrovascular incidents and myocardial infarction related to bromocriptine therapy and the consequences for the children of these patients as the mothers are unable to breastfeed. The safety of bromocriptine treatment during pregnancy has already been assessed by a survey of 1400 pregnant women who took bromocriptine primarily in the first few weeks of pregnancy and found no increased rate of abortion or congenital malformations (9). There has been some concern that PPCM patients in developing countries treated with bromocriptine will no longer be able to breastfeed. This may increase the risk of malnutrition and infection in their infants. The survival rate of infants of PPCM patients was not affected, and no serious illnesses were reported; Despite the very small number of studied children (12).

Normal weight gain from birth to 3 months of age was observed in all infants and it was normal during the 6-month follow-up period in those for whom data were available. Study results suggested no disadvantage to the infant of a PPCM patient who could not breastfeed because of bromocriptine treatment (9). Apart from its prolactin blocking role, bromocriptine may exert additional "off-target effects" in PPCM patients. Effects of bromocriptine on hemodynamic parameters in patients with heart failure were described before the treatment with ACE inhibitors and B-blockers. Positive effects of bromocriptine on blood pressure, vascular resistance, and plasma norepinephrine levels have been also described (10). Moreover, bromocriptine has been shown to increase stroke volume index and to decrease LV filling pressure (13). These potential beneficial effects of bromocriptine on hemodynamic parameters remains to be elucidated in contemporary patients with heart failure treated with B-blockers. Peripartum cardiomyopathy patients treated with bromocriptine showed significantly improved LV ejection fraction and heart failure symptoms. Importantly, in these patients, EMPs was significantly decreased compared to PPCM patients with standard heart failure therapy alone (11,12). Moreover, EMPs was significantly decreased in patients treated with bromocriptine in contrast to patients with PPCM who only received heart failure therapy (4).

Interventions

If a patient is dependent on inotropes despite optimal medical therapy, she should be transferred to a facility where intra-aortic balloon pump counterpulsation, ventricular assist devices, and transplant consult teams are available. Use of aortic counterpulsation and implantation of an assist device should be discussed with specialists. For women presenting with symptoms and severe LV dysfunction 6 months following first presentation, despite optimal medical therapy and QRS duration>120 ms, most clinicians would advise cardiac resynchronization therapy or implantable

cardioverter-defibrillator (ICD) treatment. Cardiac transplantation should be reserved for patients where mechanical circulatory support is not possible or not desirable for individual reasons or for patients who do not recover after 6-12 months on mechanical circulatory support. Patients with PPCM have a similar prognosis after transplantation to patients with DCM (8).

Conclusion

PPCM is a serious disease with high mortality and morbidity. Some conditions such as preeclampsia can be the precipitating factor for PPCM, which is not so uncommon. Some novel diagnostic markers like EMPs are effective in early disease diagnosis. Conventional heart failure treatment can be useful but bromocriptine has been proved to be a good, safe, and effective drug in PPCM.

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Conflict of Interest

The authors declare no conflict of interest.

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