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Association of peripartum cardiomyopathy with psychiatric disorders – a narrative review

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Summary

Peripartum cardiomyopathy (PPCM) is a myocardial disease characterized by a decrease in left ventricular ejection fraction below 45%, developing at the end of pregnancy or within a few months after its termination. It is a condition with multifactorial etiology that remains incompletely elucidated. Presumed pathophysiological mechanisms include excessive oxidative stress and abnormal prolactin and tryptophan metabolism. These mechanisms may also underlie the development of psychiatric disorders, which occur more frequently in patients with PPCM than in women without the condition. Studies show that PPCM patients are characterized by mental deterioration and a higher risk of diseases such as depression and schizophrenia. Since bromocriptine indirectly inhibits prolactin secretion, the important role of this drug in the treatment of PPCM is highlighted. Recent studies also highlight the potential risks of using psychiatric drugs in patients with cardiovascular burden resulting from PPCM. This article provides an overview of current knowledge on the relationship between peripartum cardiomyopathy and psychiatric disorders.

Key words: peripartum cardiomyopathy, mental disorders, depression

Introduction

Cardiomyopathies are a heterogeneous group of diseases that are characterized by abnormalities in the functioning of the heart muscle, accompanied by a change in the structure of this organ. At the same time, the presence of coronary artery disease, valvular defects, hypertension or congenital heart defects is not found to cause this abnormality. There are many types of cardiomyopathies including peripartum cardiomyopathy (also called postpartum cardiomyopathy) [1]. Peripartum cardiomyopathy

(PPCM) is a disease of the heart muscle in which there is a decrease in left ventricular ejection fraction (LVEF) below 45%. The condition is diagnosed at the end of pregnancy or within a few months after delivery, in situations where no other causes of heart failure with reduced LVEF are found [2]. Symptoms of PPCM are similar to those of left ventricular heart failure and include dyspnea when lying down and paroxysmal nocturnal dyspnea. On physical examination, patients with PPCM may present with symptoms such as excessive dilatation of the external jugular veins, tachycardia, shifting of the apical beat to the left, or peripheral edema [3]. The incidence of PPCM varies significantly geographically. The incidence of PPCM varies significantly geographically, ranging from 0.5 to 100 cases per 10,000 live births [1, 2].

Complications of peripartum cardiomyopathy include pulmonary edema, the need for mechanical circulatory support or heart transplantation, as well as complications arising from hypercoagulability associated with pregnancy and venous stasis [2]. There is also a risk of developing dilated cardiomyopathy as a consequence of PPCM. The chance of spontaneous recovery in cases of PPCM is about 50% [4]. Because of the potential for severe arrhythmias, such as ventricular fibrillation and ventricular tachycardia, PPCM is seriously life-threatening [2].

The mortality rate associated with PPCM, like the incidence of the disease, varies widely and depends on factors such as geographic region, race and length of follow-up. Women of African descent and those living in countries with lower levels of economic development show higher mortality rates. In addition, a higher percentage of deaths is observed in groups with longer follow-up, such as for several years after delivery, compared to periods limited to hospitalization. Depending on the factors mentioned above, the mortality rate associated with PPCM ranges from 0% to 50% [1–3].

Predisposing factors for perinatal cardiomyopathy, with an unknown causal relationship, include maternal age over 30 years, twin pregnancy, multiple births, African descent, maternal hypertension, previous psychiatric disorders and use of psychotropic drugs, and the presence of cardiac arrhythmias [5–7]. In addition, an association between the occurrence of PPCM and genetic mutations has been demonstrated [6].

Recent studies have drawn attention to the link between the occurrence of perinatal cardiomyopathy and the presence of psychiatric disorders. There is only a putative pathomechanism linking these conditions [8].

Purpose and method

In this study, on the basis of current medical knowledge, the authors attempt to analyze the interrelationship between peripartum cardiomyopathy and the psychiatric problems that most often coexist with it. For this purpose, an analysis of PubMed, Scopus, and Embase databases was performed using the phrases: “peripartum cardiomyopathy”, “postpartum cardiomyopathy”, and “depression”, “anxiety”, “post-traumatic stress disorder”, “psychosis”, “schizophrenia”, “mental health”. 433 records

were found, of which 259 turned out to be duplicates. Of the remaining 174 results, those that did not present the relationship between PPCM and mental disorders were excluded. Based on titles and abstracts, 137 publications were excluded, and after analysis of whole texts, another 26 items were excluded. Finally, 11 research papers were included in the review. In addition, papers related to the pathophysiology of mental disorders and peripartum cardiomyopathy were described in order to present a potential common pathomechanism. The selection process of the publications used to develop the review is illustrated in Figure 1.

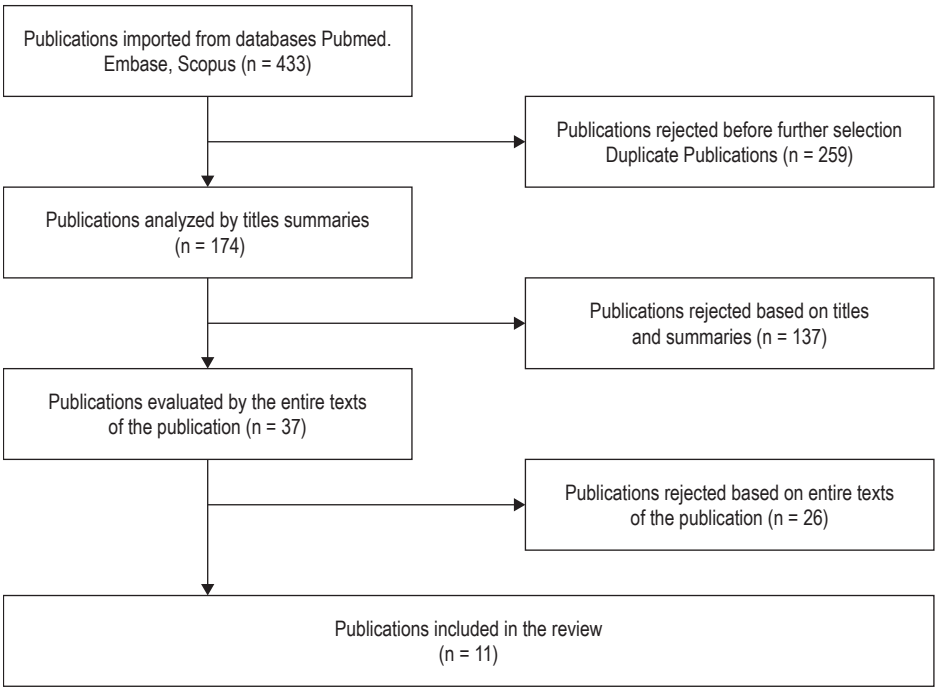

Figure 1. **Diagram for the selection of scientific publications that were included in the article**

Pathophysiology

Based on data from a rodent study, the putative pathophysiological mechanism linking perinatal cardiomyopathy occurring in mice to anxiety and depressive symptoms is based on the activity of cathepsin D, an enzyme activated by oxidative stress. Cathepsin D cleaves prolactin (which is produced in large quantities by the pituitary gland at the end of pregnancy and during lactation) to a 16 kDa fragment. This fragment

exhibits proapoptotic properties against vascular endothelial cells, reduces vasodilation dependent on these cells, and has an anti-angiogenic effect, leading to myocardial capillary damage and the development of PPCM. The study by Hilfiker-Kleiner et al. [9] also showed that the risk of damage caused by a 16 kDa prolactin fragment is higher with reduced expression of the STAT3 (Signal Transducer and Activator of Transcription 3) protein in mice. This is because STAT3 stimulates the synthesis of manganese-dependent superoxide dismutase, which neutralizes free radicals, reducing the formation of the cardiotoxic breakdown product prolactin [9]. A study by another group of researchers in rats showed that the supply of exogenous prolactin fragments ranging from 14 kDa to 18 kDa induced behaviors indicative of anxiety and depression in rodents [10].

Excessive oxidative stress, resulting from, among other things, the body's impaired ability to neutralize reactive oxygen species, plays a key role not only in the pathogenesis of PPCM, but also in the development of symptoms of depression, post-traumatic stress disorder (PTSD), and anxiety disorders. A potentially common pathophysiological mechanism could explain the link between PPCM and the aforementioned psychiatric disorders [11–13].

Elevated plasma levels of kynurenine and free circulating microRNA (ribonucleic acid) – miR-30e, were observed in patients with concurrent peripartum cardiomyopathy and psychiatric disorders, while serotonin levels were reduced. High kynurenine levels and low serotonin levels are associated with impaired tryptophan metabolism. Under physiological conditions, tryptophan is converted to serotonin, but in patients with PPCM, this pathway is impaired, and tryptophan is converted to kynurenine. Impaired tryptophan metabolism may be associated with the onset of depressive states, while increased kynurenine levels have been observed in schizophrenia and other psychiatric disorders. In addition, as a result of the body's response to the development of heart disease, there is likely to be a release of miR-30e, which inhibits the function of the 5-hydroxytryptamine receptor 1a (5-HT1a), responsible for the transmission of serotonin. Inhibition of this pathway may explain the presence of depressive symptoms in PPCM patients, providing a mechanism linking the two disease entities [14].

Emotional problems in PPCM patients

The occurrence of depressive and anxiety symptoms and impaired quality of life in patients with peripartum cardiomyopathy has been described in a few studies. In some cases, they can be so intense and disturbing that their presence entitles them to a clinical diagnosis. Mukona et al. [15] presented results obtained from semi-structured interviews conducted with six patients diagnosed with PPCM. The results showed that the patients experience significant psychological strain. The diagnosis of PPCM is often perceived as shocking, triggering a depressive mood and feelings of fear and uncertainty. The women fear death and leaving their children behind, which further increases their

emotional distress. In addition, the diagnosis affects their family planning decisions, limiting the possibility of having more children, which is a source of frustration and sadness. The psychological burden is also associated with financial and professional difficulties, as some women lose their jobs as a result of health problems. Psychosocial support, both from the family and health care professionals, plays a key role in alleviating these difficulties. The importance of religious support and faith were also identified as important factors in helping female patients cope with their illness [15].

In another study, structured clinical interviews were used to analyze the mental state of 19 patients diagnosed with perinatal cardiomyopathy. The obtained data were analyzed, which showed that 17 of the studied patients experienced feelings of anxiety and fear [16].

A study by Rosman et al. [17] provides additional information on the psychological stress and quality of life of patients after PPCM. They studied 149 women at various times since diagnosis, using tools such as the Generalized Anxiety Disorder-7 (GAD-7), Cardiac Anxiety Questionnaire (CAQ), and Medical Outcomes Study Short Form 12 (SF-12) Health Survey. Clinically significant levels of anxiety were noted in 53% of subjects. Particularly elevated anxiety scores were observed in patients who had recently been diagnosed with PPCM.

Mental disorders in patients with PPCM

The co-occurrence of psychiatric disorders along with perinatal cardiomyopathy has been described in relatively few studies. One of them analyzed medical data from 48 patients who experienced peripartum cardiomyopathy, The control group consisted of patients with similar demographic and clinical data without a diagnosis of this disease. The study found that patients with diagnosed anxiety disorders are more likely to experience PPCM [18].

The second study involved determining the interrelationship between perinatal cardiomyopathy and psychiatric disorders based on structured interviews and laboratory data. This study analyzed the data of 40 patients diagnosed with PPCM who were compared with postpartum women who were not diagnosed with the disease. Structured clinical interviews were conducted and blood levels of kynurenine, serotonin, and miR-30e were measured. Twenty-six patients (60% of the subjects) in the PPCM group were diagnosed with psychiatric disorders such as depression, adjustment disorder, PTSD, and generalized anxiety disorder. In comparison, these disorders were present in only 11.6% of perinatal women without concurrent PPCM. The analysis showed a statistically significant increase in the prevalence of the aforementioned psychiatric disorders (with the exception of generalized anxiety disorder, which occurred less frequently in the study group than in the control group) in patients with perinatal cardiomyopathy. In addition, patients with PPCM were characterized by greater severity of depressive symptoms as assessed by the Beck scale. The results regarding the levels of kynure-

nine, serotonin, and miR-30e were discussed earlier in this article, in the subsection on pathophysiology [14].

Another study analyzed the data of more than 119,000 women giving birth between 2007 and 2019. Patients who had been diagnosed with cardiovascular disease before pregnancy (except hypertension), patients with twin pregnancies, and women who did not have valid medical insurance throughout the study period (for 24 months after delivery) were excluded from the analysis. The incidence of perinatal cardiomyopathy, heart failure, coronary heart disease, stroke, arrhythmias (including sudden cardiac arrest), and hypertension in women with and without postpartum depression were compared. The results were presented in the form of a hazard ratio (HR), where the co-occurrence of postpartum depression was the differentiating factor between the study groups. HR values were adjusted for a variety of potentially relevant variables, such as maternal age, the presence of depression, diabetes or hypertension before pregnancy, obesity, and smoking. The analysis showed that the adjusted risk ratio exceeded 1 for each analyzed cardiovascular disease. For cardiomyopathy, the HR was 1.61, the second highest score after ischemic heart disease (HR = 1.83). The study showed no significant relationship between hypertension comorbidity and psychiatric disorders [19].

The research design by Rosman et al. [7] included 177 patients diagnosed with peripartum cardiomyopathy, in whom the intensity of depressive symptoms was checked. The severity of depressive symptoms was assessed using the Patient Health Questionnaire Depression Scale – 8 (PHQ-8), with a mean score of 8.27 ± 6.86, with clinically significant depression diagnosed in 32.3% of the subjects. The authors of the study paid particular attention to the need for patients to follow medical recommendations. These recommendations included regular follow-up visits, adherence to pharmacotherapy, adherence to a low-fat and low-sodium diet, smoking cessation, giving up alcohol, and regular physical activity. The majority of patients (≥87.7%) followed most of the recommendations, but only 50.9% followed a low-fat and low-sodium diet, and only 18.7% exercised regularly. Adherence to these recommendations reduces the risk of future cardiovascular events and improves overall health, while non-adherence increases the risk of depression and increased medical costs [7].

Other researchers have also stressed the importance of patients' regular cooperation in their adherence to medication. In the following study, the degree of adherence to medical recommendations by patients with PPCM was assessed on the basis of an analysis of prescription fulfillment and indicators of the presence of prescribed drugs in the patients' blood, as assessed by high-resolution mass spectrometry. Patients taking every prescribed drug were classified into the adherent group, while those taking only some of the prescribed drugs were classified into the partially adherent group, and those not taking any drug – into the non-adherent group. The subjects' health status was assessed using the EQ-5D-5L (European Quality of Life – 5 Dimensions – 5 Levels) and HADS-A/D (Hospital Anxiety and Depression Scale) scales. The results

indicated that patients in the group of completely adhering to medical recommendations show lower severity of depressive symptoms and anxiety compared to patients who partially adhered to the recommendations or did not adhere to them at all [20].

A study published in 2020 looked at determining the relationship between post-traumatic stress and depression and the quality of life of women with PPCM, which was investigated using Impact of Event Scale (IES) questionnaires, where most of the 28 surveyed women indicated that they feel a strong or severe impact of PPCM on their lives, and all patients were screen-diagnosed with depression using the Center for Epidemiology Scale – Depression (CES-D). The severity of depressive symptoms correlates positively with the level of stress resulting from the trauma [21].

A retrospective study by Wolfe et al. [22] analyzed medical data of patients hospitalized between 1999 and 2015 to determine the prevalence of various characteristics in a population of women who experienced perinatal cardiomyopathy. The results were compared with a control group with similar demographic, clinical, and obstetric characteristics. The prevalence of diagnosed, previous or current psychiatric disorders was similar in both groups, but there was an increased prevalence of depressive symptoms among women with PPCM. These women also have a higher prevalence of anxiety-related symptoms.

A broader perspective of the analyzed problem is presented assessing the quality of life and mental health of women who experienced heart disease during pregnancy and in the first 12 months after delivery. Patients were recruited through social media (Facebook) and cardiology facilities, which allowed 43 women to be surveyed. The study did not specify the specific disease entities from which the patients suffered. Women with heart disease during pregnancy and in the first year after delivery reported reduced quality of life, and questionnaire results showed the presence of symptoms of depression, anxiety, and stress. On the Depression, Anxiety, and Stress Scales-21 (DASS-21), 24% of the surveyed patients achieved scores indicative of moderate, severe, or very severe depression, while 22% of patients achieved elevated scores on the anxiety scale, and 19.5% on the stress scale. Patients diagnosed with cardiac disease during pregnancy present higher depression and stress parameters, while women diagnosed with heart disease before pregnancy show higher levels of anxiety. On the CAQ scale, 44.5% of patients achieved at least moderate levels of anxiety [23].

PPCM therapy methods with mental well-being in mind

As mentioned above, an important element in improving the mental state of a PPCM patient is compliance with medical recommendations. According to Hoevelmann et al. [20], proper education plays an important role in patient care, especially for women living in poorer developing countries, where PPCM occurs more frequently. There is also a need for appropriate, systemic solutions to facilitate adherence [7, 20]. Similar results on the benefits of medication adherence in the therapeutic process were presented

by Rosman et al. [7], as discussed in the section on mental disorders in patients with PPCM. Based on these two articles, it can be concluded that adherence to medical recommendations is a key component of effective therapy.

Drugs used to treat PPCM include those standardly used to treat other forms of heart failure. These include beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), and preload-reducing drugs such as aldosterone antagonists, loop diuretics, and nitrates. Note that ACEIs and ARBs have a high teratogenicity, so they are contraindicated in pregnancy. Particular caution should be exercised during therapy with loop diuretics, as their use can reduce placental blood flow. Among beta-blockers, selective beta-1 receptor antagonists are preferred in pregnant women, as beta-2 receptor blockade can induce uterine contraction activity. Drugs with a high safety profile in pregnancy include digoxin, hydrochlorothiazide, and chlorothiazide, which can be included in the treatment of peripartum cardiomyopathy even before termination of pregnancy. The authors also point out the possibility of using levosimendan in the treatment of PPCM, but its effect on pregnancy is currently under discussion. Another group of drugs that has found use in PPCM therapy are anticoagulants. Their use is sometimes necessary because patients with the disease often develop thromboembolic complications. Examples of a drug in this group include warfarin, which is contraindicated in pregnancy, and low-molecular-weight heparins, which have no teratogenic effects and can therefore also be used in pregnancy [2, 24].

In the context of psychiatric disorders co-occurring with peripartum cardiomyopathy, special attention should be paid to psychiatric drugs that prolong the QT interval. Their use requires special caution, as QT interval prolongation poses a risk of fatal arrhythmias, such as torsade de pointes [25]. For this reason, in women with PPCM who are given drugs that prolong the QT interval, it is absolutely necessary to monitor the ECG, and if the interval is found to be prolonged, it is necessary to reduce the dose or discontinue the cardiotoxic drug altogether. In such a situation, it is possible to use a drug from the benzodiazepine group or electroconvulsive therapy. The implantation of a subcutaneous cardioverter-defibrillator, which reduces the risk of sudden cardiac death due to arrhythmia, or the wearing of a defibrillation vest should also be considered [26].

A particularly interesting drug used in the treatment of perinatal cardiomyopathy is bromocriptine, the use of which seems justified due to its inhibition of prolactin secretion, which can have a significant impact on the development of PPCM [9]. However, caution should be exercised when using this drug, as there are reports that bromocriptine can induce psychosis, particularly in patients with a psychiatric history [27]. However, it is worth noting that the use of bromocriptine is rarely associated with mental deterioration, as confirmed by clinical practice.

Recapitulation

Peripartum cardiomyopathy is a rare heart disease that occurs at the end of pregnancy or up to several months after and is characterized by a decrease in left ventricular ejection fraction. The incidence of this disease varies by geographic region, and risk factors include advanced maternal age, African descent, and hypertension, among others. It is an interesting disease entity from a psychiatric perspective as well. Of interest is the association of PPCM with psychiatric disorders, particularly depression. It is speculated that the process of prolactin cleavage by cathepsin D, activated by oxidative stress, is responsible for such a condition, so one effective treatment for PPCM is the use of bromocriptine, a drug that indirectly reduces prolactin production. In women diagnosed with PPCM, special attention should be paid to mental status and appropriate treatment of both cardiomyopathy and possible psychiatric disorders should be implemented, while keeping in mind the fact that a significant proportion of psychiatric drugs prolong the QT interval, which can promote life-threatening arrhythmias. An increased prevalence of depressive symptoms, often requiring treatment, has been observed among women with PPCM. A factor that also has a significant impact on health is adherence to medical recommendations, such as following a low-sodium and low-fat diet, discontinuing stimulants, exercising regularly, taking medications as prescribed by a doctor and showing up regularly for follow-up appointments. Introducing systemic solutions that could help PPCM patients meet the above requirements, especially in developing countries, is a challenge for the healthcare system.

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