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PERIPARTUM CARDIOMYOPATHY: CURRENT UNDERSTANDING OF PATHOPHYSIOLOGY, DIAGNOSIS, TREATMENT, AND MATERNAL-FETAL OUTCOMES

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Abstract: Goal: To provide a comprehensive and up-to-date review of the pathophysiology, diagnosis, treatment and outcomes of Peripartum Cardiomyopathy. Methods: A narrative bibliographic review was carried out using the PubMed database, with the search terms "Peripartum Cardiomyopathy", "Diagnosis", "Management" "Treatment", "Risk Factors", "Pathophysiology", combined with Boolean terms "AND" and "OR". The results found were 430 articles, of which 16 were selected to form the basis of the research. **Discussion**: The study that peripartum cardiomyopathy (PPCM) is of great clinical importance, as it is a major contributor to maternal morbidity and mortality worldwide, in addition to directly affecting fetal health. As a form of diagnosis, the measurement of markers (focusing on BNP and NT-proBNP) associated with imaging tests (echocardiogram, electrocardiogram and biopsy, depending on the case) is recommended.
Although the choice of treatment varies according to the patient's clinical condition, bromocriptine stood out as the main drug choice in the vast majority of cases. However, some women may develop a more severe form of the disease, thus requiring more invasive and aggressive intervention.
Final considerations: Continuous research is crucial to improve clinical management, especially in genetic and immunological investigation and identification of additional risk factors, so that the diagnosis and management of MCPP can be improved in the future.
Keywords: Peripartum cardiomyopathy, pathophysiology, diagnosis, treatment.

INTRODUCTION

Peripartum Cardiomyopathy (PPCM) is a distinct clinical entity that was initially described in the 19th century, but only began to be more thoroughly investigated in

1971 (LINDLEY K.J. et al., 2019). It is a rare form of heart failure that manifests itself at a crucial stage in a woman's life, having serious implications for both the mother and the fetus (BAUERSACHS J. et al. 2019). The prevalence of PPCM varies substantially based on racial/ethnic and geographic factors. For example, populations of African and African-American origin have a higher incidence, ranging from 1:100 to 1:299 pregnancies, while in Denmark, the incidence is 1:10,000. In the United States, the incidence varies between 1:1000 and 1:4000 births, possibly reflecting the trend of increasing maternal age and the occurrence of multiple pregnancies (DAVIS M.et al. 2020).

PPCM presents a challenging diagnosis due to the overlap of its symptoms with typical manifestations of a normal pregnancy or other forms of heart failure. This overlap can result in delays in diagnosis and intervention, exacerbating associated complications. The underlying pathophysiology involves a range of factors, including genetic components, anomalous immunological reactions, hormonal imbalances, angiogenic disturbances, and possible nutritional deficiencies, such as selenium deficiency (IORGOVEANU C. et al., 2021).

Given the complexity of PPCM and the significant impact on maternal and fetal health, it is imperative to deepen understanding of this condition. Awareness and understanding of risk factors and pathological mechanisms are crucial to improving early diagnosis, clinical management and, eventually, outcomes for affected patients (BALA R. et al., 2023).

This review sought to provide a comprehensive and up-to-date analysis of Peripartum Cardiomyopathy, supported by recent scientific evidence and clinical guidelines. Emphasis was placed on epidemiology, pathophysiology, diagnosis, and therapeutic options, with a particular focus on the impact on maternal and fetal health. Additionally, recent advances in understanding the underlying molecular and cellular mechanisms, as well as emerging strategies for effective clinical management of PPCM, were explored.

METHODOLOGY

This is a narrative bibliographic review based on the PVO strategy, an acronym that represents: population or research problem, variables and outcome, with the guiding question "What are the pathophysiological mechanisms underlying Peripartum Cardiomyopathy in women in the peripartum period, and how do these mechanisms influence maternal-fetal clinical outcomes after different treatment approaches, based on recent scientific evidence and clinical guidelines?". From this perspective, the population referred to in the research is women in the peripartum period, that is, the period that covers the end of pregnancy, childbirth and the immediate postpartum period. Furthermore, the variable analyzed was: the pathophysiological mechanisms underlying the pathology, including hemodynamic, hormonal and immunological changes, with the research outcome examining the maternal and fetal outcomes associated with this condition, in addition to evaluating clinical outcomes after different treatment approaches. for pathology, including recovery rate of cardiac function and quality of life. The search was carried out in the PubMed Central (PMC) database. The search terms used were "Peripartum Cardiomyopathy", "Diagnosis", "Management" "Treatment", "Risk Factors", "Pathophysiology", which were combined with the Boolean terms "AND" and "OR". The results found were 430 articles, which were subsequently submitted to the selection criteria. The inclusion criteria were: articles in the English language, published between 2019 and 2023, that addressed the themes proposed

by this research and those that answered the guiding question. Therefore, studies such as review articles, meta-analysis, randomized clinical trials and observational studies were included. The exclusion criteria were: duplicate articles, which did not directly address the proposal studied and which did not meet the other inclusion criteria. Therefore, a total of 16 articles were selected to compose this study.

DISCUSSION

Peripartum cardiomyopathy (PPCM) is a disease of great clinical relevance, being one of the main contributors to maternal morbidity and mortality rates globally. This condition is associated with several clinical complications, including decompensated heart failure, thromboembolic events, arrhythmias and mortality, which emphasizes the importance of understanding its predisposing factors for early diagnosis (HOEVELMANN J. et al., 2022a).

According to Bala R. et al. (2023), the incidence of MCPP in the United States ranges from 1 in 1,000 to 1 in 4,000 live births. An analysis of approximately 64 million North American hospital records identified 34,219 cases, with an incidence of 1 in 968 births, corroborating previous estimates. Globally, the highest incidence was observed in Nigeria and Haiti, with rates of 1 in 100 and 1 in 300 live births, respectively, and the lowest in Japan, with a rate of 1 in 15,000. The prevalence of MCPP is often underestimated due to underreporting and demographic variations. Furthermore, defining reliable diagnostic criteria is a challenge, making large-scale prospective observational studies essential to establish an accurate incidence (BALA, R. et al., 2023).

Peripartum cardiomyopathy is directly involved in maternal and fetal health, thus impacting morbidity and mortality rates. It is estimated that this pathology may have a mortality rate of 10%, in addition to causing a greater probability of recurrence in future pregnancies (BALA, R. et al., 2023). This rate may vary according to countries, reaching 4% in developed countries and 14% in developing countries (HOEVELMANN, J. et al., 2021). From a prognostic point of view, the rates are quite varied, ranging from 21% to 61% over a 6-month period. Over a period of 4.5 years, less than half of the patients developed a Left Ventricular Ejection Fraction (LVEF) greater than 50%, indicating myocardial dysfunction (KOERBER, D. et al., 2023). Therefore, MCPP can result in compromised quality of life due to its morbidity and mortality.

Regarding morbidity aspects, peripartum cardiomyopathy results in a reduction in the Left Ventricular Ejection Fraction of less than 45%, in addition to other cardiac changes such as increased atrial pressure, increased pulmonary pressure and ventricular dilation (BALA, R. et al., 2023). According to Berliner, D. et al. (2023), an impairment of right ventricular function was detected in the vast majority of women. However, PPCM allows for a high recovery rate if treated appropriately, reaching 72% after 12 months, varying from 46-63% in the first few months. However, according to Koerber, D. et al. (2023), lower recovery rates can be observed, reaching only 21% in the first 6 months, in addition to a greater risk of death from sudden tachyarrhythmias in patients diagnosed with this pathology. Therefore, some prognostic methods were implemented in an attempt to predict the recovery rate of patients with PPCM.

Several risk factors for MCPP are well established. According to Iorgoveanu C. et al. (2021), they include ethnicity, with a higher incidence in African and African-American populations compared to Caucasians; pre-eclampsia; prolonged use of tocolytics; maternal age over 30 years; multiparity;

multiple pregnancies; and nutritional status. Selenium deficiency in Nigerian women, for example, has been identified as a risk factor (BALA, R. et al., 2023).

Therefore, the pathophysiology of MCPP is complex and involves multiple mechanisms, such as hemodynamic stress of pregnancy, vascular and hormonal factors, inflammation and genetic components (BALA, R. et al., 2023).

Bauersachs J. et al. (2019) point out two pathophysiological pillars: systemic angiogenic imbalance and host susceptibility. Recent studies suggest that 15-20% of patients with MCPP have mutations in genes associated with cardiomyopathies. Furthermore, the cleavage of prolactin into an antiangiogenic subfragment under conditions of oxidative stress contributes to endothelial damage and cardiomyocyte dysfunction. There is also overlap between vascular complications of pregnancy, such as pre-eclampsia, and MCPP, possibly due to common mechanisms involving inhibitors of vascular endothelial growth factors (BAUERSACHS J. et al., 2019). However, MCPP is still considered an idiopathic cardiomyopathy associated with pregnancy due to uncertainty regarding its pathophysiological mechanisms (BALA, R. et al., 2023).

Through studies, it became possible to establish some parameters capable of helping to evaluate the consequences of this pathology. Patients with a higher baseline LVEF, higher blood pressure levels and a smaller end-diastolic diameter (54.19–58.37 mm) would have a higher recovery rate, while an increased end-systolic diameter would be deleterious for the patient and associated with mortality rates. (HOSSEINPOUR, A. et al., 2022). In addition to these values, the impact of NT pro-BNP on the prognosis and recovery of these patients was evaluated; values of this marker equal to or greater than 900 pg/ml indicated a lower probability of recovery of LVEF, normal levels of LV end-diastolic diameter (less than 55 mm) and, consequently, a lower chance of recovery of left ventricular function (HOEVELMANN, J. et al., 2021). In this line of reasoning, these data can be used as prognostic predictors of peripartum cardiomyopathy.

For Adedinsewo D.A. et al. (2023), it presents an innovative approach to screening for peripartum cardiomyopathy using artificial intelligence (AI) as a diagnostic tool in clinical settings. The importance of accurate and effective screening methods for this cardiac condition is highlighted, which is often underdiagnosed in high-risk populations, as is the case in Nigeria. The use of AI allows the analysis of clinical data and biomarkers in real time, offering the possibility of early identification and, consequently, more effective therapeutic intervention. This advancement represents a significant leap forward from traditional diagnostic methods, which often rely on subjective assessments and diagnostic tests that can be invasive or expensive. Therefore, the integration of AI into peripartum cardiomyopathy screening emerges as a promising strategy to improve clinical outcomes in this population.

A multidisciplinary approach is crucial to identifying and treating this condition effectively.

This may include the use of cardiac imaging, such as echocardiography, as well as biomarker analysis and genetic testing to assess risk in specific populations. Furthermore, the article highlights that screening strategies can vary significantly according to regional guidelines and available resources, which makes a global consensus imperative to optimize patient care (HOEVELMANN J. et al., 2022a).

For the diagnosis of peripartum cardiomyopathy, clinical guidelines recommend the measurement of certain biochemical markers, as well as the

performance of imaging tests. BNP values below 100 pg/ml or NT-pro BNP values below 300 pg/ml are crucial to exclude the diagnosis of heart failure (HF), since these markers tend to remain elevated in cases of peripartum cardiomyopathy (MCPP). Additional tests, such as echocardiogram and electrocardiogram, may be necessary, and in some situations, myocardial biopsy may be indicated (BALA R. et al., 2023). According to Hoevelmann J. et al. (2021), the preferred markers for detecting HF in the postpartum and during pregnancy are atrial natriuretic peptides, including BNP and NT-pro BNP, corroborating what was proposed by Bala R. et al. (2023). Once the diagnosis has been established, it is imperative to initiate appropriate therapy with the aim of improving the patient's prognosis.

Most medications used in cases of peripartum cardiomyopathy (PPCM) are also applicable in patients with heart failure (HF). Standard treatment includes bromocriptine, which promotes ventricular recovery over a period of six months, typical medications for HF, anticoagulation with heparin during pregnancy and heparin or warfarin postpartum. Furthermore, angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB), contraindicated during pregnancy, are indicated in the postpartum period (BALA R. et al., 2023). The association of bromocriptine with standard HF therapy can optimize left ventricular recovery and reduce mortality and morbidity rates when compared to patients who do not use this medication (BERLINER D. et al., 2023). More aggressive therapies may be necessary in severe cases of MCPP.

Treatments vary in different aspects and stages of evolution of peripartum cardiomyopathy. Sliwa K. et al. (2021) describe treatment in the subacute gestational phase as similar to that of patients outside the peripartum period, avoiding angiotensin-converting enzyme (ACE) inhibitors due to their deleterious effect on the fetus, angiotensin receptor blockers (ARB), angiotensin receptor inhibitors angiotensin-neprilysin (ARNI) and mineralocorticoid receptor antagonists.

During pregnancy, the BOARD regimen (bromocriptine, oral therapy for heart failure, anticoagulation [heparin], vasorelaxant agents and diuretics) is recommended, and in the postpartum period, the use of ECA/ARB is allowed, associated with the continuation of heparin or warfarin until significant recovery of left ventricular (LV) function (BALA R. et al., 2023). Notably, more than 80% of ACE/ARB prescriptions were associated with a reduction in 12-month all-cause mortality and improved LV recovery (HOEVELMANN J. et al., 2022a).

There is consensus between the studies and the European Society of Cardiology (ESC) Guidelines, as stated by Sliwa K. et al. (2021), on the use of bromocriptine. However, its use at the beginning of treatment may worsen symptoms, reflected by lower blood pressure and left ventricular ejection fraction (LVEF). These rates are similar to those in women not treated with bromocriptine, according to Tremblay-Gravel et al. (2018), but show improvement when analyzing the general prognosis, according to Haghikia A. et al. (2018).

Women treated with bromocriptine showed a more significant recovery of cardiac function compared to those not treated with the medication (TREMBLAY-GRAVEL M. et al., 2018). This is because the treatment offers a high probability of complete right ventricular (RV) and LV recovery, with 58% of all patients with RV dysfunction achieving complete cardiac recovery in addition to standard heart failure medication, regardless of treatment duration (HAGHIKIA A. et al., 2018).

Treatment time showed variation in

different studies. After childbirth, the use of bromocriptine must be considered, as it inhibits lactation. It has been suggested to increase the use of bromocriptine in specific circumstances, where the potential to strengthen LV functional recovery in the medium and long term would outweigh the benefits of breastfeeding. Studies indicate that, with the use of bromocriptine, LVEF changes over the course of treatment, initially from 23 ± 10% to 55 ± 12%, and from 30 ± 12% to 45 ± 13% at 6 months (TREMBLAY- GRAVEL M. et al., 2018).

Selenium was the subject of study due to its broad spectrum of biological effects and because it is a critical component of central antioxidant enzymes such as glutathione peroxidases (GPX). The risk of the primary composite endpoint of persistence of heart failure symptoms and LV systolic dysfunction was not significantly reduced by selenium supplementation. However, it significantly reduced symptoms of heart failure (KARAYE K.M. et al., 2020). Finally, the studies also describe the use of levosimendan as an alternative inotropic and mechanical circulatory support (MCS), in addition to ventricular assist devices in patients with cardiogenic shock (SLIWA K. et al. 2021).

Recommendations for childbirth are also addressed, pointing out that up to 10% of patients with peripartum cardiomyopathy may require a heart transplant (BALA R. et al., 2023).

Not all patients respond to conventional treatment, requiring more invasive approaches. Some women may progress to severe forms of HF, making it necessary to monitor central venous pressure, pulmonary artery catheterization, and the use of inotropic and vasopressor drugs. About 10% of women with MCPP require heart transplantation, a procedure more common in high-income countries (18%) compared to low-income countries (3%) (BALA R. et al., 2023; Koerber D. et al., 2023). In cases of advanced HF, some patients may require mechanical circulatory support, with the use of left ventricular assist devices (BERLINER D. et al., 2023). Therefore, to reduce morbidity and mortality associated with MCPP, early diagnosis and appropriate treatment, adapted to the severity of the clinical condition, are crucial.

FINAL CONSIDERATIONS

This review addressed Peripartum Cardiomyopathy (PPCM), a clinical condition of notable complexity and relevance. The importance of early diagnosis and personalized treatments was highlighted, especially the promise of the BOARD regimen during pregnancy and the use of ACE inhibitors/ARBs postpartum. Treatment varies depending on the stage of the disease, and the high morbidity and mortality associated with PPCM reinforces the need for multidisciplinary strategies. Continued research is vital to improving the clinical management of PPCM. Areas such as genetic and immunological research, as well as the identification of new risk factors, are crucial to advance the diagnosis and treatment of this condition. Ultimately, this review aims to contribute to progress in the recognition, management and prevention of PPCM, with the aim of improving patients' quality of life and ensuring safer pregnancies for mothers and fetuses.

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