New Insights in Peripartum Cardiomyopathy

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KEYWORDS

- Peripartum cardiomyopathy • Pregnancy • Cardiac disease
- Congestive heart failure

KEY POINTS

- Specific diagnostic criteria should be used to diagnose peripartum cardiomyopathy (PPCM), but this is a diagnosis of exclusion.
- Although rare, PPCM is a leading cause of maternal mortality.
- Significant advances have been made in understanding PPCM pathophysiology, especially hormonal and genetic mechanisms.
- Long-term and recurrent pregnancy prognosis depends on recovery of cardiac function.

INTRODUCTION

Peripartum cardiomyopathy (PPCM), or heart failure (HF) associated with pregnancy, was first described in 1937.[1] The syndrome was poorly defined until 1971 when specifically noted as occurring in the peripartum period.[2] Hibbard and colleagues[3] included echocardiographic (ECHO) criteria for PPCM in 1999, stressing reduced ejection fraction (EF <45%) toward the end of pregnancy or in the months postpartum in women without structural heart disease,[4] although some women may present earlier.[5] Incidence, 1:1000 to 1:4000 live births in the United States,[6] varies by geographic location[7,8] and has been increasing in the United States.[9–12] PPCM is a leading cause of maternal mortality.[13–17] Long-term consequences include chronic HF and transplantation. Recent advances based on animal models, registries, and genetic/biomarker testing have shed light on pathways promising more specific diagnosis, improved risk stratification, and targets for specific therapy.

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PROPOSED PATHOGENIC MECHANISMS

Investigation of the pathophysiology of PPCM is limited by its rare incidence and lack of specific diagnostic markers. Postulated mechanisms include hemodynamic stress of pregnancy, viral myocarditis, fetal microchimerism, and malnutrition.[18]

The theory that PPCM results from idiopathic dilated cardiomyopathy (DCM) precipitated by the hemodynamic stress of pregnancy is limited by the fact that hemodynamic changes reach near maximum by the end of the second or early third trimester before peak PPCM incidence.[19] Similarly, although myocarditis was proposed as an important mediator, the prevalence of abnormal endomyocardial biopsy specimens has varied widely and is not clearly different from controls.[20,21]

An autoimmune hypothesis developed from evidence that hematopoietic cells introduced into maternal circulation due to pregnancy-related immunosuppression are attracted to cardiac tissue, later recognized as non-self, leading to a pathologic response.[22] However, migration of multipotential fetal stem cells may mitigate injury.[23] Malnutrition (eg, selenium deficiency) could magnify PPCM development in some populations but has not been described widely.[24] Other associations include prolonged tocolysis, although β-mimetic tocolysis has diminished.[25] Novel proposed associations include anemia, asthma, and substance abuse,[26] but these may provoke HF through different mechanisms.

Hormonal/Vascular Derangements

Current research focuses on hormonal shifts occurring peripartum coinciding with the peak incidence of PPCM.[6] Both prolactin and soluble FMs-like tyrosine kinase-1 (sFlt1) have been implicated in PPCM pathogenesis.[27,28] An imbalance in angiogenic factors appears to promote PPCM.

Antiangiogenic fragments of prolactin derived from pituitary gland can result in cardiac apoptosis, vascular dropout, and systolic dysfunction.[28] Hilfiker-Kleiner and colleagues[27] noted that female mice with cardiomyocyte-specific deletion of the STAT3 gene developed PPCM. The role of STAT3 is cardioprotective, upregulating antioxidant enzymes such as manganese superoxide dismutase (MnSOD). In the absence of STAT3, cathepsin D cleaves prolactin into a 16-kDa fragment, which promotes apoptosis with subsequent left ventricular (LV) dysfunction. The 16-kDa fragments induce endothelial cells to package microRNAs into lipid-encapsulated particles, which suppress the neuregulin/ErbB pathway, required for cardiomyocyte function and viability.[29] Treatment with bromocriptine, inhibiting prolactin production, rescued the mice, thus preventing PPCM.[27] Biopsy tissue from PPCM patients undergoing transplant showed lower levels of STAT3 activity, and 16-kDa fragments were detected in serum of patients with PPCM.[27]

In a second model, mice lacking proliferator-activated receptor-gamma coactivator-1α (PGC1-α) developed PPCM.[28] PGC1-α, a transcriptional coactivator that drives mitochondrial biogenesis, is highly expressed in the heart, upregulates MnSOD, and regulates angiogenic factors, including vascular endothelial growth factor (VEGF).[30] Absence of PGC1-α leads to reduced antioxidant activity and increased reactive oxygen species with cleavage of prolactin into the 16-kDa fragment.[28] Treatment with VEGF in this model improves outcomes, but treatment with both VEGF and bromocriptine is required for complete rescue. In this model, 2 pathways lead to PPCM.[28]

Late pregnancy is associated with an antiangiogenic environment due to placental secretion of factors such as sFlt1.[28] The heart secretes local VEGF, but this is insufficient to prevent development of PPCM. In this model, administration of sFlt1 is sufficient to cause cardiomyopathy outside of pregnancy.[28] Placental secretion of sFlt1 is