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Editorial

The Thyroid Axis in Peripartum Cardiomyopathy: A Potential Contributor to a Multifaceted Disease

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See article by Kouzu et al., page 796.e1–796.e3 of this issue.

Peripartum cardiomyopathy (PPCM) is diagnosed when new-onset heart failure with reduced ejection fraction occurs in the last months of pregnancy—or in the months following delivery—in the absence of an alternative cardiomyopathy diagnosis. Recognizing that PPCM has a wide spectrum of clinical manifestations, with some forms occurring earlier in pregnancy and others having only a subtle decrease in left ventricular function, strict timing and ejection fraction cutoffs were abandoned in the latest iteration of diagnostic criteria by the European Society of Cardiology.[1] This effort to broaden diagnostic criteria aims to reflect heterogeneity in disease phenotypes but also to counteract PPCM underdiagnosis, as it is associated with a high morbidity burden, even in high-income settings in California, where it remains an important cause of maternal mortality in the contemporary era.[2]

The past decades have brought fascinating insights into the mechanistic construct of PPCM. Akin to other forms of idiopathic cardiomyopathy, PPCM carries a high prevalence of pathogenic genetic variants known to cause dilated cardiomyopathy. However, PPCM also distinctly involves susceptibility to extracardiac factors related to the hormonal milieu of pregnancy, as well as hemodynamic stressors related to uterine flow and delivery. The unpredictability of clinical presentation and chances of recovery are likely the result of the specific combination of factors at play in each case. As research progresses and more mechanistic to phenotypic correlations are made, there is general agreement that PPCM will be further classified according to the etiological triggers, with distinct clinical presentations, individual prognostic features, and— eventually—tailored therapeutics.

In this issue of the *Canadian Journal of Cardiology*, the case description of Kouzu et al.[3] greatly exemplifies the multisystemic nature of PPCM. They report a typical case of peripartum cardiomyopathy in a woman who developed heart failure and reduced ejection fraction several months after her second delivery. Uncommonly, she concomitantly had elevated free triiodothyronine (T3) and thyroxine (T4) serum levels, a suppressed thyroid-stimulating hormone (TSH), positive thyroid peroxidase antibody titers, and reduced iodine uptake compatible with destructive, autoimmune thyroiditis. With cessation of lactation, treatment with bromocriptine, recovery of an euthyroid state, and—perhaps most importantly—time, left ventricular function recovered fully.

As many women develop autoimmune thyroiditis without heart failure in the postpartum period, thyrotoxicosis cannot be the sole factor causing PPCM. Adhering to the concept of multiple hits, it is possible that hyperthyroidism was the necessary additional factor unmasking cardiomyopathy in the case presented. A definite association between hyperthyroidism and PPCM has not yet been established; however, several pathophysiology hypotheses merit exploration. Known myocardial effects of T3 and T4 include increased contractility and lusitropy via expression of proteins involved in intracellular calcium flux, decreased vagal tone, and excessive adrenergic response.[4] Early in the disease course, an increase in cardiac output is observed; however, long-term untreated hyperthyroidism causes excessive cardiac workload, leading to hypertrophy and high-output heart failure. Systolic heart failure has also been reported in numerous settings including stress cardiomyopathy,[5-7] possibly due to heightened sensitivity to catecholamines common to both conditions. Uninodular, multinodular, or diffuse goiter, as well as thyrotoxicosis, have been previously associated with a PPCM diagnosis in 1337 women in the United States,[8] supporting the association between hyperthyroidism and PPCM.

The pathologic hormonal changes specific to PPCM include increased cleavage of prolactin into proapoptotic vasoinhibins and excessive placental-derived sFlt1 secretion, known for its antiangiogenic properties.[9] Of note, animal models suggest increased production of such

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proinflammatory vasoinhibins, via increased cathepsin D activity, in the presence of T3.[10] Although these effects have not been confirmed in women with PPCM, further attention should be directed at the impact of excessive T3 levels on protein regulation within fragile myocytes as well as the interplay between suppressed TSH and high prolactin levels in the postpartum period, both of which are anterior pituitary hormones. Other endocrine disorders—such as preexisting diabetes, a condition in which downregulation of vascular endothelial growth factor has been observed—are associated with a higher incidence of PPCM.[11]

The authors highlight the potentially heightened effect of prolactin in PPCM associated with hyperthyroidism, given mechanistic plausibility and based on the patient's full recovery only after the addition of bromocriptine. Although the cause-to-effect relationship between bromocriptine and recovery must be observed critically, we agree that prolactin blockade should be considered in such patients after careful evaluation of potential benefits and risks. Whether bromocriptine should be used in all cases of PPCM remains debatable, as there is a lack of definite superiority over medical therapy alone in appropriately controlled randomized trials. Moreover, whether bromocriptine should be used only when faced with nonrecovery has not been studied and would not be readily supported by the current understanding of PPCM mechanisms. At present, high serum prolactin levels are not a prerequisite to initiate bromocriptine therapy.[12]

A diagnosis of PPCM requires the exclusion of other causes of cardiomyopathy, but guidelines do not detail which baseline workup must be obtained. The Canadian Cardiovascular Society Heart Failure guidelines suggest measuring TSH in all patients with new-onset heart failure,[13] a recommendation that could be transferrable to all patients with PPCM. Although we do not believe that postpartum thyroiditis should preclude asserting a diagnosis of PPCM, but rather should help define the PPCM phenotype, we do think that a TSH assay should be obtained in the baseline PPCM workup, even in the absence of clinical suspicion. In the same vein, the most recent Heart Failure Society of America guidelines on genetic evaluation of cardiomyopathy recommend genetic counselling and family screening for all women with PPCM, whether or not family history is present.[14] An effort to identify a maximal number of etiological hits in every woman with PPCM is a step toward delivering more individualized treatment. A multidisciplinary approach is key, including endocrinologists as in the case presented, as well as genetic counsellors, obstetricians, and pediatricians.

In conclusion, the observations by Kouzu et al. highlight the multisystemic nature of PPCM and demonstrate the importance of ensuring thyroid axis integrity in all patients. Gathering all disease contributors can help identify therapeutic targets as part of a personalized approach to treating PPCM. The role of the thyroid axis in the peripartum state deserves attention in current PPCM registries and mechanistic studies.

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