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Editorial

Editorial: How do genetic components play a role in peripartum cardiomyopathy?

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Peripartum cardiomyopathy (PPCM) is a rare, but life-threatening condition that occurs during the peripartum period in previously healthy women. Recently used diagnostic criteria included an idiopathic cardiomyopathy presenting with heart failure secondary to left ventricular systolic dysfunction (left ventricular ejection fraction <45%) toward the end of pregnancy or in the 5–6 months following delivery, where no other cause of heart failure was found [1]. Since it is a diagnosis of exclusion, heterogeneity is a common element in the pathogenesis of PPCM. Therefore, several theories have been proposed for the pathophysiological mechanism underlying the development of PPCM, including antiangiogenic agents such as fragmented prolactin [2] and soluble fms-like tyrosine kinase-1 (sFLT1) [3], autoimmune disorder [4], viral myocarditis [5], and pregnancy-induced cardiac stress.

Van Spaendonck-Zwarts et al. reported that a subset of PPCM is an initial manifestation of familial dilated cardiomyopathy (DCM) [6]. Morales et al. also reported that a proportion of PPCM and pregnancy-associated cardiomyopathy cases results from a genetic cause [7]. Those reports more strongly supported the suggestion that some cases of PPCM may in fact be part of familial DCM. Actually, titin gene mutations are found to be common in families with both DCM and PPCM [8]. However, the workshop held by the US National Heart Lung and Blood Institute and the Office of Rare Diseases concurred that PPCM is a distinct entity, rather than a clinically silent underlying cardiomyopathy unmasked by the hemodynamic stresses of pregnancy, because the reported incidence of PPCM is higher than the incidence of idiopathic cardiomyopathy [9].

Among pregnant women with underlying heart disease, heart failure has been described typically at the end of the second trimester, or after delivery [10]. During pregnancy, especially by the end of the second trimester, cardiac output increases by 30–50%, where increase in plasma volume leads to increase in stroke volume and heart rate. Patients with stenotic lesions or severely decreased cardiac function cannot tolerate such increased preload, and therefore are likely to suffer from heart failure. Delivery is considered another particularly high-risk period because of cardiac stress and short-term dramatic changes in cardiac output caused by pain, uterine contractions, bleeding, anesthesia, autotransfusion from the involuting uterus, and resorption of edema. Those hemodynamic changes can cause heart failure in pregnant women with heart disease, including preexisting DCM. However, the onset of heart failure in PPCM tends to occur in later postpartum compared to the above timing. This point is one of the reasons why many of the PPCM cases cannot be explained only by the hemodynamic stresses for underlying other cardiomyopathy.

PPCM with mutations of titin gene showed a low rate of recovery (only 2 of 20 PPCM patients showed a full recovery of left ventricular function) [8]. However, the cardiac function is often normalized in many PPCM patients. For example, PPCM complicated with pregnancy-associated hypertension showed a better recovery rate than those without hypertension [11]. From this point of view, many of PPCM cases must be distinguished from underlying DCM.

There have been a number of reports in the literature of PPCM in women with mothers or sisters who had the same diagnosis without a family history of DCM. In this issue of the journal, Canpolat et al. reported about four cases of PPCM in the same family [12]. Interestingly, they showed full recovery of left ventricular function within a short period. In such cases, other genetic origins, which are unrelated to DCM, may play a role in the onset of PPCM.

Several PPCM animal models have been examined. For example, female mice with a cardiomyocyte-specific deletion of stat3 were reported to develop PPCM. In these mice, cardiac cathepsin D expression and activity is enhanced by increased oxidative stress in the cardiomyocyte. Cathepsin D activity is associated with the generation of a cleaved antiangiogenic and proapoptotic 16 kDa form of the nursing hormone prolactin, which may contribute to deterioration of PPCM (Fig. 1) [2]. Another mouse model that lacked cardiac PGC-1α, a powerful regulator of angiogenesis, was reported to develop profound PPCM [3]. From these results, a systemic angiogenic imbalance is considered one pathophysiology for PPCM. Importantly, these PPCM mice models are entirely rescued by pro-angiogenic therapies. Therefore, genetic factors related to peripartum angiogenic insufficiency have a possibility to cause the familial PPCM.

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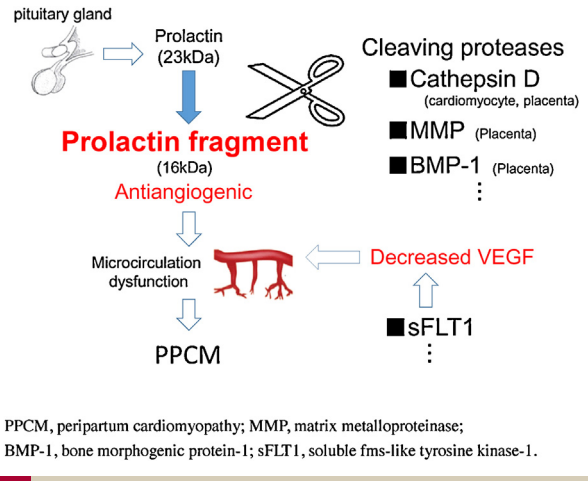

Fig. 1. Angiogenic imbalance theory. PPCM, peripartum cardiomyopathy; MMP, matrix metalloproteinase; BMP-1, bone morphogenic protein-1; sFLT1, soluble fms-like tyrosine kinase-1.

Preeclampsia is a pregnancy-related disease that is characterized by high blood pressure and proteinuria, and also known as the major risk factor of PPCM. Lately, the mechanism of preeclampsia has been understood further. The placentas of preeclampsia patients show aplasia of the helicine artery, which induces increased production of many antiangiogenic factors such as sFLT1. Antiangiogenic factors cause maternal vascular endothelial dysfunction and result in elevated blood pressure and renal dysfunction. Preeclampsia is known to have familial occurrence, too. Therefore, genetic factors, which relate to both preeclampsia and PPCM, can exist.

Few data are available with which to formally evaluate any genetic contribution to susceptibility to PPCM and the studies that have been published are largely case reports rather than systematic studies. Lately, next-generation sequencing approach is used widely to analyze human genes. In the near future, such technology will allow the evaluation of the common variants, which contribute to PPCM susceptibility.

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