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Relaxin-2 and Soluble Flt1 Levels in Peripartum Cardiomyopathy

Results of the Multicenter IPAC Study

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ABSTRACT

OBJECTIVES This study explored the association of vascular hormones with myocardial recovery and clinical outcomes in peripartum cardiomyopathy (PPCM).

BACKGROUND PPCM is an uncommon disorder with unknown etiology. Angiogenic imbalance may contribute to its pathophysiology.

METHODS In 98 women with newly diagnosed PPCM enrolled in the Investigation in Pregnancy Associated Cardiomyopathy study, serum was obtained at baseline for analysis of relaxin-2, prolactin, soluble fms-like tyrosine kinase 1 (sFlt1), and vascular endothelial growth factor (VEGF). Left ventricular ejection fraction (LVEF) was assessed by echocardiography at baseline and 2, 6, and 12 months.

RESULTS Mean age was 30 ± 6 years, with a baseline of LVEF 0.35 ± 0.09. Relaxin-2, prolactin, and sFlt1 were elevated in women presenting early post-partum, but decreased rapidly and were correlated inversely with time from delivery to presentation. In tertile analysis, higher relaxin-2 was associated with smaller left ventricular systolic diameter ($p = 0.006$) and higher LVEF at 2 months ($p = 0.01$). This was particularly evident in women presenting soon after delivery ($p = 0.02$). No relationship was evident for myocardial recovery and prolactin, sFlt1 or VEGF levels. sFlt1 levels were higher in women with higher New York Heart Association functional class ($p = 0.01$) and adverse clinical events ($p = 0.004$).

CONCLUSIONS In women with newly diagnosed PPCM, higher relaxin-2 levels soon after delivery were associated with myocardial recovery at 2 months. In contrast, higher sFlt1 levels correlated with more severe symptoms and major adverse clinical events. Vascular mediators may contribute to the development of PPCM and influence subsequent myocardial recovery. (Investigation in Pregnancy Associate Cardiomyopathy [IPAC]; NCT01085955) (J Am Coll Cardiol HF 2016;4:380–8) © 2016 by the American College of Cardiology Foundation.

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Peripartum cardiomyopathy (PPCM) is characterized by the development of heart failure late in pregnancy or in the months after delivery (1). Incidence varies geographically and in the Unites States is estimated at 1 in 1,000 to 4,000 live births (2–6). Presentation, clinical course, and outcomes are heterogeneous and can be associated with significant morbidity and mortality (1). In a recent prospective, multi-center study of 100 women with PPCM (IPAC [Investigations in Pregnancy Associated Cardiomyopathy]), 13% of patients suffered major events or had persistent severe cardiomyopathy (7). Factors associated with poorer outcomes include left ventricular (LV) dilation, severely depressed LV systolic function, black race, later presentation, and greater body mass index (7–10).

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The etiology of PPCM is unknown. Suggested causes include genetic predisposition, hormonal abnormalities, abnormal immune response, and inflammation (11,12). Recently, it has been proposed that biological mediators with hemodynamic or vascular effects that are produced in the pregnant or peripartum state may play a role in the pathogenesis of PPCM (13–15). One of these factors is relaxin-2, a hormone produced in the corpus luteum of the ovary and in the heart (16,17). Relaxin-2 increases during pregnancy with hemodynamic and vasoactive effects, including increased cardiac output, plasma volume, heart rate, and renal blood flow and lower vascular resistance (18). In addition, relaxin-2 has anti-inflammatory, angiogenic, and antifibrotic properties (16). Both the vasodilatory and angiogenic effects of relaxin-2 are mediated in part by vascular endothelial growth factor (VEGF) (19,20), which may exert a protective effect in heart failure of multiple etiologies (21). This understanding has led to investigation of relaxin as a therapeutic target in heart failure (22) and raises the possibility of a role in treatment of PPCM.

Another biological factor proposed to contribute to PPCM is prolactin, a pituitary hormone that is secreted in the peripartum period and stimulates lactation (23). Under conditions of oxidative stress, prolactin is cleaved proteolytically to a 16-kDa fragment that has deleterious effects on endothelial cells and promotes inflammation and fibrosis. Higher levels of this angiostatic fragment, and the resulting angiogenic imbalance in the myocardium, have been hypothesized to play a role in the pathophysiology of PPCM (24). Another anti-angiogenic factor released from the placenta and endothelial cells in mid to late pregnancy is soluble fms-like tyrosine kinase 1 (sFlt1 or VEGF receptor 1). sFlt1 peaks at delivery and inhibits the activity of VEGF, leading to endothelial dysfunction and further angiogenic imbalance (14,25). Increased levels of sFlt1 may play an important role in the development of PPCM in some women (14,15), and recent data suggest that therapy targeting these pathways can rescue mouse models of PPCM (14,26). We report the analysis of relaxin-2, prolactin, sFlt1, and VEGF levels and their relationship to recovery of LV function and clinical outcomes in the IPAC cohort.

ABBREVIATIONS AND ACRONYMS

BP = blood pressure

GLM = general linear model

LV = left ventricular

LVAD = left ventricular assist device

LVEF = left ventricular ejection fraction

NYHA = New York Heart Association

PPCM = peripartum cardiomyopathy

sFlt1 = soluble fms-like tyrosine kinase 1

VEGF = vascular endothelial growth factor

METHODS

COHORT. As previously reported, 100 women with newly diagnosed PPCM were enrolled at 30 centers (Online Appendix) between December 1, 2009 and September 30, 2012. All women were at least 18 years of age and had no previous history of cardiac disease, an estimated clinical LV ejection fraction (LVEF) of ≤0.45, and an evaluation consistent with nonischemic cardiomyopathy. Women with significant valvular disease, coronary disease, bacterial septicemia, ongoing drug or alcohol abuse, history of chemotherapy or chest radiation within 5 years, or a history of a previous cardiomyopathy were excluded.

PROTOCOL. The study protocol was approved by the institutional review boards at all participating centers, and informed consent was obtained from all subjects. At the time of enrollment, demographic information, including self-designated race, previous clinical evaluation, and current medical therapy, was recorded. Women were followed until 1 year post-partum. All hospitalizations and major cardiac events including death, cardiac transplantation, or implantation of a LV assist device (LVAD) were recorded.

LV FUNCTION. All subjects had an echocardiogram to assess LVEF at the time of enrollment and at 6 and 12 months post-partum. In addition, women enrolled early (within 6 weeks post-partum, n = 66) had a repeat assessment of LV function at 2 months. LV volumes and LVEF were assessed in a core laboratory (University of Pittsburgh) using biplane Simpson's rule with manual tracing of digital images. LV end-diastolic diameter and LV systolic diameter were assessed in the parasternal long axis view. A subset of studies (22 of 310, 7%) were not available for assessment by the core laboratory due to format, and the LVEF calculated locally was used.