Vasoinhibin Serum Levels Are Required to Demonstrate Their Role in Peripartum Cardiomyopathy Etiopathology

To the Editor:

Wiedemann *et al*. report a case of a patient with peripartum cardiomyopathy (PPCM) and hyperprolactinemia who received a biventricular assist device and was treated with cabergoline.[1] They conclude that patients with severe PPCM might benefit from treatment with cabergoline and suggest proactive testing of pregnant women for hyperprolactinemia and consideration of early treatment with cabergoline before any signs of heart failure. The authors state that the prognostic or therapeutic implications of hyperprolactinemia are completely unknown. However, they should have acknowledged the various studies addressing a pathophysiological role of prolactin in PPCM, as well as the evaluation of dopamine D2 agonists for the treatment of PPCM. A study published in 2007 introduced the hypothesis that an antiangiogenic prolactin fragment with a molecular mass of 16 kDa (defined as 16 kDa vasoinhibin isoform[2]) is a key pathological mediator of PPCM.[3] The study reported that this vasoinhibin would impair myocardial microvascularization and, thereby, contribute to myocardial dysfunction. Accordingly, a new therapeutic approach for PPCM was developed using the dopamine D2 receptor agonists, cabergoline and bromocriptine. The concept underlying this putative therapy is the inhibition of vasoinhibin generation by substrate depletion, that is, the inhibition of pituitary prolactin secretion by activation of dopamine D2 receptors in lactotrophs. Subsequently, several articles have been published,[4–6] reviewing the available evidence, describing signaling mechanisms mediating the deleterious action of the 16 kDa vasoinhibin isoform and supporting the beneficial effects of treatment with dopamine D2 agonists in patients with PPCM. Treatment with bromocriptine is currently being evaluated in a multicenter clinical trial (NCT00998556).[7]

Testing of pregnant women for hyperprolactinemia and consideration of early treatment with cabergoline before any signs of heart failure, as suggested by the authors, is not a rational approach for the early prevention of vasoinhibin-related onset of PPCM. This is because hyperprolactinemia occurs physiologically toward the end of pregnancy and postpartum, and the relatively low incidence of PPCM prohibits dopamine D2 receptor agonist treatment without prior risk stratification or onset of clinical symptoms. Instead, the determination of vasoinhibin serum levels by a semiquantitative methodology combining immunoprecipitation and western blotting[8] seems to be a more adequate tool for the risk stratification of these patients because an increase in vasoinhibin serum levels preceding the onset of PPCM would be expected. Ideally, a quantitative vasoinhibin assay could be developed, which should then be used to confirm altered levels of vasoinhibin isoforms in PPCM.

The patient described by Wiedemann *et al*. exhibited only a modest elevation of prolactin levels (28.9 ng/ml), which could also have been physiological or stress-related. Conversely, modest hyperprolactinemia may reflect prolactin conversion to vasoinhibins, which have reduced crossreactivity in prolactin immunoassays.[9,10] Without further evidence, such as vasoinhibin levels, or any other related proof, the beneficial effect of cabergoline treatment in their patient cannot be ascertained.

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