Imbalanced Angiogenesis in Peripartum Cardiomyopathy (PPCM)

To the Editor:
In their report on imbalanced angiogenesis in peripartum cardiomyopathy (PPCM), Mebazaa et al concluded that low sFlt-1/PlGF ratio may be used to diagnose PPCM. We would like to caution against this conclusion. It is important to note that the timing of measurements of the reported factors, soluble FLT-1 (sFLT-1), relaxin-2, and placental growth factor (PIGF), and the ratio of sFLT-1 to PIGF is critical.

The authors derive their conclusions from comparing levels of sFlt1 and PlGF in plasma from postpartum women with PPCM (n=83) vs. 2 control groups: healthy women at delivery (n=30), and patients with acute heart failure (AHF: n=65). With respect to the first control group, the timing of measurements is critical. Soluble Flt1 is released from placental trophoblasts, and its levels increase throughout pregnancy. Once the placenta is delivered, sFlt1 levels decrease relatively quickly but not instantaneously. Powers et al estimated the decrease of sFlt1 levels to be 2.5%/h, equivalent to a half-life of 27 h. More recently, Wathen et al carefully demonstrated a biphasic decrease in sFlt1 levels, with a rapid half-life of 3.4 h followed by a slow one of 29 h. The blood draws from the PPCM subjects in the Mebazaa et al study are reported to have taken place at a median time of 4 weeks postpartum (range 3.4–4.6 weeks). By this time, sFlt1 levels can be expected to have returned to non-postpartum, non-pregnant levels. In sharp contrast, blood draws from the healthy women control group took place within 24 h of delivery, when sFlt1 levels can be expected to still be high. Comparison between women with PPCM 3–4 weeks after delivery vs. healthy women at delivery is therefore not valid.

With respect to the second control group (i.e., patients with AHF), it is critical to note that this group contains patients on average twice the age of women in the PPCM group, and more than one-half are men. Comparison between these 2 groups is thus also not valid. Indeed, in their Table S3, the authors report that sFlt1 levels and sFlt1/PlGF ratio are lower in women than in men, and in fact similar to the numbers seen in their PPCM cohort.

In an earlier report, Damp et al showed that serum sFlt1 levels measured in 100 PPCM subjects, the largest prospective study of PPCM published to date, were significantly higher when sampled from 0 to 11 days postpartum. These higher levels, in the range of 539±621 pg/mL, correlated significantly with major adverse clinical events and severity of HF classification. Serum levels rapidly declined after 11 days postpartum. Thus, high sFlt1 levels in PPCM, when measured early postpartum, indicate a worse prognosis, rather than ruling out PPCM as suggested by Mebazaa et al. In the same study, relaxin-2 levels were also shown to be much higher in days 0–11 postpartum and to rapidly decline thereafter. Higher relaxin-2 levels in the early postpartum period were associated with recovery of left ventricular ejection fraction at 2 months postpartum.

In summary, it is impossible to draw conclusions about serum or plasma levels of sFLT1, PlGF, and relaxin-2 in PPCM patients unless the samples are taken during pregnancy or immediately postpartum, given the rapid decline in levels after delivery. Valid conclusions about any results must be drawn from cases and controls matched for age, sex, and gestational age or time postpartum.

References

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