Peripartum cardiomyopathy (PPCM) is a relatively rare but potentially life-threatening heart disease associated with pregnancy. It is defined as a non-familial peripartum heart failure characterized as an idiopathic cardiomyopathy secondary to left ventricular systolic dysfunction that emerges towards the end of pregnancy or in the first months postpartum in previously healthy women, where no other cause of heart failure is found. Clinically, PPCM resembles a dilated cardiomyopathy (DCM), although the left ventricle may not always be dilated, and the ejection fraction is nearly reduced below 45%. PPCM is considered as an independent disease, diagnosed by its relation to pregnancy and the exclusion of other cardiomyopathies.

In this issue of the Journal, Mebazaa et al report that the plasma concentrations of proangiogenic factors, including placenta growth factor (PIGF), an antiangiogenic factor, soluble fms-like-tyrosine-kinase receptor 1 (sFlt-1), and their ratio (sFlt-1/PIGF), can distinguish patients with PPCM from healthy nonpregnant women and nonpregnant women with acute heart failure (AHF). The incidence of PPCM is reported to vary among different geographic regions: 1 in 300 in Haiti, 1 in 1,000 in South Africa, 1 in 1,000-4,000 in the USA, but less in European countries and Japan: 1 in 10,000-15,000. Such differences have been explained by ethnicity, genetic diversity, socio-economic changes, increased diagnostic yield and increasing awareness of the disease created such by the Working Group on PPCM of the Heart Failure Association of the European Society of Cardiology and the IPAC Study group in the USA.

Although its etiology remains unknown, potential risk factors include hypertensive disorders during pregnancy (e.g., preeclampsia), advanced maternal age, multiparity, multiple gestation, and African descent. The increased incidence in particular geographical regions suggests that genetic predisposition might have an important role. A subset of patients with PPCM have been identified as carriers of mutations associated with familial forms of DCM, involving mutations such as TNN truncating variants. Therefore, some patients with PPCM might, in fact, be presenting with an initial manifestation of familial DCM. Epidemiological studies have indicated that PPCM in women with a family history of DCM show a lower recovery rate than those without such a background: a feature that might affect risk stratification and clinical management of such patients.

Oxidative stress is caused by an imbalance between reactive oxygen species (ROS) production and capacity to detoxify ROS. The level of oxidative stress rises during pregnancy, and oxidative damage increases in late pregnancy; organ-specific antioxidant defense mechanisms are particularly important in the peripartum phase. In the heart, expression of antioxidant enzymes, such as mitochondrial superoxide dismutase (SOD2) is increased. The major signaling pathways responsible for the upregulation of SOD2 include activator of transcription 3 and peroxisome proliferator-activated receptor γ coactivator 1α.

Table. Imbalance of Angiogenic Factors in Patients With PE During Pregnancy, Those With PPCM Without Preeclampsia After Delivery, HN and AHF Nonpregnant

<table>
<thead>
<tr>
<th>Condition</th>
<th>sFlt-1</th>
<th>sFlt-1/PIGF</th>
<th>PIGF</th>
<th>PGC 1α</th>
<th>16 kDa</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>→</td>
<td>→</td>
<td>↑↑</td>
</tr>
<tr>
<td>PPCM</td>
<td>↑</td>
<td>↑↑↑</td>
<td>→</td>
<td>→</td>
<td></td>
</tr>
<tr>
<td>HN</td>
<td>→</td>
<td>→</td>
<td>↑↑↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHF</td>
<td>↑</td>
<td>↑↑↑</td>
<td>→</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

16 kDa, 16-kDa prolactin; AHF, acute heart failure; HN, healthy nonpregnant; PE, preeclampsia; PGC 1α, peroxisome proliferator-activated receptor γ coactivator 1α; PIGF, placenta growth factor; PPCM, peripartum cardiomyopathy; sFlt-1, soluble fms-like-tyrosine-kinase receptor 1. (Adapted from references 1, 3 and 7.)
proliferator-activated receptor γ coactivator 1α (PGC-1α). The precise balance between oxidative and antioxidant capacities in late pregnancy and early postpartum is critical to maintaining maternal health. If the balance is compromised, the increased oxidative stress may predispose to PPCM.

Early in pregnancy a balance of proangiogenic and antiangiogenic factors is established in the developing placenta. Proangiogenic factors include vascular endothelial growth factor (VEGF), PlGF, PGC-1α and their Flt-1 receptors. In addition, a splice variant of Flt-1, sFlt-1, is expressed in the placenta and has antiangiogenic effect by binding VEGF in the extracellular space. Angiogenic imbalance such as overproduction of sFlt-1 is thought to initiate preeclampsia. Because preeclampsia sometimes predisposes to PPCM, sustained overproduction of sFlt-1 is thought to be a cause of PPCM. PPCM occurring in late pregnancy or early postpartum might be triggered by such factors specifically present in the late-gestational period.

Prolactin is among the prominent hormones in the peripartum phase, and large quantities of prolactin are released from the pituitary gland into the circulation during lactation. Prolactin can exert opposing effects on angiogenesis: the full-length 23-kDa form is a proangiogenic factor, but a 16-kDa derivative, which is generated by matrix metalloproteinases (MMPs), is a potent antiangiogenic factor. The role of 16-kDa prolactin in PPCM is supported by studies showing that the serum level of MMP-2 is significantly higher in women with PPCM than in matched pregnant controls. A clinical trial using standard therapy for heart failure in PPCM, including β-blockers8 in combination with suppression of prolactin release using the D2 dopamine-receptor agonist bromocriptine in order to reduce the antiangiogenic prolactin 16-kDa derivative, is currently being performed in Germany.

In line with the pro- and antiangiogenic factors during pregnancy and the peripartum and postpartum phases mentioned above, changes and imbalance of the proangiogenic factors, VEGF, PI GF and PGC-1α, and antiangiogenic factors, sFlt1 and 16-kDa prolactin, have been implicated as biomarkers of preeclampsia and PPCM. For example, high maternal plasma sFlt1/PIGF values have been shown to be associated with preeclampsia and stillbirth and are thought to be a risk factor for the development of PPCM. However, Mebazza et al demonstrate that in postpartum PPCM patients the sFlt1/PIGF ratio is rather lower, PI GF is higher and sFlt1 is similar compared with nonpregnant AHF patients. Furthermore, postpartum PPCM patients have lower sFlt1/PIGF ratio and sFlt1 values and a similar PI GF value compared with healthy pregnant women; in addition their sFlt1/PIGF ratio and sFlt1 are lower and PI GF similar compared with healthy pregnant women at delivery (Table).

The differences in the imbalance of angiogenesis of postpartum PPCM patients between the present study by Mebazza et al9 and previous studies1,6,7 obviously derive from the former only enrolling patients from South Africa where prepartum PPCM is rare; thus, patients with cardiac failure associated with any form of hypertension, including preeclampsia, were excluded. So, the diagnostic value of placenta growth factor and imbalanced angiogenesis might not apply in other countries, and further studies are necessary to confirm generalized markers of PPCM.1,3,7 A recent nationwide database analysis in Japan that dealt with hospitalization and mortality by heart failure failed to include PPCM patients, because the study only enrolled patients with ICD10 codes I and K; the ICD10 code for PPCM belongs to O. Cardiologists should start taking care of prepartum and postpartum patients earlier in order to detect and treat PPCM; for example, in Japan it was reported that more than 60% of PPCM patients were initially seen by an obstetrician when they complained of heart failure symptoms; less than 10% were primarily managed by a cardiology specialist.10

Disclosures
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References

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