European Heart Journal (2014) **35**, 680–682
doi:10.1093/eurheartj/eht485

EDITORIAL

Possible joint pathways of early pre-eclampsia and congenital heart defects via angiogenic imbalance and potential evidence for cardio-placental syndrome

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Online publish-ahead-of-print 2 December 2013

This editorial refers to 'Maternal and foetal angiogenic imbalance in congenital heart defects'†, by E. Llurba *et al.*, on page 701

Foetal vasculogenesis and angiogenesis and maternal angiogenesis are essential requirements for a pregnancy. Decidua-associated vascular changes arise in the inner junctional zone myometrium in early pregnancy, followed by trophoblast invasion with associated remodelling.[1] Decidual natural killer and dendritic cells regulate key developmental processes at the human foetal–maternal interface via human leucocyte antigen (HLA)-C, HLA-E, and HLA-G.[2] Intervillous flow starts at 7–8 weeks gestation, via connecting channels between maternal myometrial spiral arteries and lacunae in the wall of the implanted cytoblast. Early trophoblast plugging might protect the embryo against high oxygen concentrations, and it has to be postulated that premature loss of those plugs could lead to early miscarriage or early-onset pre-eclampsia.[3]

In the past decade, extensive research has investigated the abnormalities that can occur in the first trimester of pregnancy that could lead to chorionic regression or small placenta, contributing to intrauterine growth restriction and early-onset pre-eclampsia.[4] Placental flow defects can occur as early as 12 weeks in women who subsequently develop pre-eclampsia. Hypoxia and reoxygenation episodes can generate reactive oxygen species, leading to placental oxidative stress and placental dysfunction. Although the causes of pre-eclampsia, defined as new hypertension (diastolic blood pressure >90 mmHg) and substantial proteinuria (>300 mg in 24 h) after 20 weeks gestation,[4] remains largely unknown, the leading hypothesis strongly suggests disturbed placental function in early pregnancy, possibly due to failed interaction between two genetically different organisms.[4] As a second stage of the foetal–maternal interphase, research by Levine and Karumanchi has shown an increased production of bioactive trophoblast debris, including an excess of syncytiotrophoblast-derived antiangiogenic factors, such as soluble forms of vascular endothelial growth factor (VEGF) receptors, including the VEGF receptor-1, also called fms-like tyrosine kinase 1 (Flt-1).[5]

This excessive systemic inflammatory response results in endothelial dysfunction and an associated increase in vascular reactivity, preceding onset of the clinical condition pre-eclampsia, which affects 2–8 % of all pregnancies.[4]

Flt-1 is expressed on endothelial cells and macrophages, and binds to VEGF and a platelet-derived protein called placental growth factor (PlGF), with a wide range of functions which are not completely understood.[6] A potential endogenous opponent of PlGF in the plasma is soluble fms-like tyrosine kinase (sFlt-1), which represents a type of Flt-1, without the transmembrane and intracellular tyrosine kinase domain. sFlt-1 and PlGF have comprehensive involvement not only in the development of atherosclerotic processes and myocardial infarction, but also in a wider range of other inflammatory processes such as sepsis, acute lung injury, and neoplasm, as recently reviewed by Hochholzer *et al.*[6]

However, most work on this interesting biomarker has been performed in pre-eclampsia. sFlt-1 can be measured in the placenta and serum of pregnant women. In normotensive pregnancy, the sFlt-1 levels are stable up to the middle stages of gestation, followed by a steady increase from 33 weeks onwards. This increase corresponds to a late-gestational decrease in free PlGF levels. It is postulated that this serves to slow placental vascular growth by increasing antiangiogenic factors such as sFlt-1, and decreasing levels of proangiogenic factors such as VEGF and PlGF.

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† doi:10.1093/eurheartj/eht389.

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In women with pre-eclampsia, this process of governing placental growth and function might occur too early, leading to endothelial dysfunction. Interestingly, these alterations in sFlt-1 and PlGF levels appear to be greatest in women with early pre-eclampsia.[5] A recent study by Govender *et al.*[7] reported a different type of angiogeneic and antiangiogenic regulation in early- vs. late-onset pre-eclampsia, with placental VEGF mRNA expression being markedly reduced in late-onset pre-eclampsia.

Maynard *et al.*[8] have shown that administration of sFlt-1 in pregnancy induced hypertension, proteinuria, and glomerular endotheliosis, mimicking the clinical syndrome of pre-eclampsia. A study in women with pre-eclampsia vs. normal controls found increased levels of sFlt-1 and reduced PlGF, beginning ~ 5 weeks before onset of pre-eclampsia, implying a pathogenic role. Those alterations were greatest in women with early-onset pre-eclampsia and small-for-gestational age infants. Interestingly, Patten *et al.*[9] showed that mice which lack cardiac PGC-1α, a powerful regulator of angiogenesis, developed a peripartum cardiomyopathy. In addition, they showed that patients with peripartum left ventricular dysfunction reported to have had pre-eclampsia while pregnant had inappropriately high levels of sFlt-1 in serum taken 4–6 weeks post-partum. Interestingly these women did not have proteinuria post-partum, which would have been expected. The persistent extraplacental source of sFlt-1 in the post-partum period is unknown, but may include placental remnants.[9]

The interesting study by Llurba and colleagues investigates the extent of angiogenesis in human heart development by investigating maternal and cord PlGF, sFlt-1, and soluble endoglin (sEng) in 65 cases of congenital heart defects (CHDs) and 204 normal controls.[10] The CHD cases consisted of isolated CHDs, such as left ventricular outflow tract obstruction due to, for example, aortic valve stenosis and coarctation of the aorta ($n = 23$), contruncal abnormalities, such as tetralogy of Fallot and transposition of the great arteries ($n = 25$), as well as atrioventricular valve defects such as septal defects or Epstein's anomaly ($n = 17$). Three women who developed severe pre-eclampsia and one woman who developed severe intrauterine growth restriction were excluded.

In addition, angiogenic factor expression and markers of hypoxia were measured in the heart tissue from 23 CHD foetuses and 8 controls. In the CHD group, sFlt-1 was significantly higher and, therefore, PlGF highly significantly lower. Foetuses with CHDs also had higher cord sFlt-1 and sEng plasma levels. Examination of the heart tissue from the foetuses with CHDs showed a significant increase in markers of chronic hypoxia and antioxidant activity, as well as expression of VEGF and sFlt-1.

The authors need to be congratulated for performing a carefully conducted, complex study presenting the first evidence of abnormal angiogenesis in the heart tissues of human foetuses with CHDs, showing increased sFlt-1 expression and overproduction of proteins, such as HIF-2α, HO-1, and SOD1 as a result of chronic hypoxia.

Flt-1 has previously been implicated in regulation of embryonic heart function and cardiac morphogensis.[11]

Interestingly, the study of Llurba *et al.* showed that, in isolated major foetal heart defects, maternal serum PlGF was deceased and sFlt1 increased at 18–37 weeks gestation, suggesting impaired placental angiogenesis. This impairment was found in the presence of conotruncal and septal valve defects but not in left heart defects, suggesting that abnormal angiogenesis may be deleterious for septal valve and outflow tract formation of human heart embryogenesis. In fact, as highlighted by the authors in their discussion, the aetiology of left-sided heart malformations is likely to be complex and includes environmental exposure and a genetic component as abnormalities in the NOTCH1 pathway.[10]

How could the abnormal angiogenic pattern in maternal blood of women carrying a foetus with CHD be explained? The data by Llurba *et al.* suggest that foetus may have an intrinsic altered angiogenesis leading to abnormal formation of the heart that may already be present in the trophoblastic cells. Often this abnormality does not allow survival of the foetus, as 20% of all stillbirths and 30% of neonatal deaths have abnormalities of the heart and great arteries. An alternative hypothesis would be that low maternal PlGF could lead to a lesser degree of trophoblast invasion of the spiral arteries, leading to placental hypoxia. The authors further speculate that placental hypoxia due to abnormal angiogenesis may cause foetal hypoxia, thus leading to abnormal heart development and low birth weight.

What is not explained by those findings is why mothers carrying a child with CHDs and presenting with elevated sFlt-1 and low VEGF and PlGF do not develop hypertension and proteinuria, as in pre-eclampsia, or even a peripartum left ventricular dysfunction as suggested by Patten *et al.*[9] Interestingly, 3 out of 71 women carrying a CHD child were excluded from the study as they developed severe pre-eclampsia.

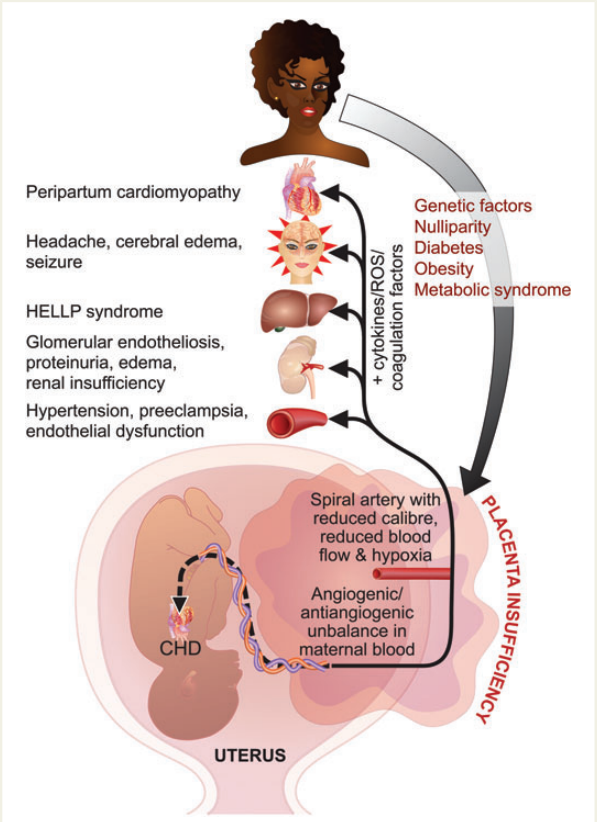

Figure 1 Angiogenic/antiangiogenic imbalance and cardioplacental syndrome. CHD, congenital heart defect; ROS, reactive oxygen species.

sFlt-1 and possibly angiogenic/antiangiogenic imbalance has a very broad and more complex function, and we assume that it is involved in several cascades. However, it is unlikely to be the sole leading factor involved in human disease such as pre-eclampsia or even peripartum cardiomyopathy in humans (*Figure 1*). High sFlt-1 levels have recently been shown to be good predictors of mortality in acute myocardial infarction, independently of other markers such as troponin T or N-terminal pro brain natriureic peptide.[6]

Hypoxia itself causes increased sFlt-1 production. The hypoxia-induced overproduction of sFlt-1 could activate a cycle wherein high sFlt-1 levels inhibit angiogenesis and exacerbate the placental hypoxia, which subsequently causes an increase in placental sFlt-1 production.[12]

Evaluation of the relationship between CHDs and placenta-related complications should be explored in further research.

In conclusion, the authors have provided significant evidence of abnormal angiogenesis associated with human CHDs. The relationship between congenital cardiac disease in the newborn, placental dysfunction, and, possibly, abnormality in the angiogenesis of the parents of those children needs to be further investigated.

Conflict of interest: none declared.

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