An integrated model of materno-foetal cardiac dysfunction in severe pre-eclampsia

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Abstract

Maternal cardiovascular deterioration in severe pre-eclampsia is due to a combination of factors in the setting of severe trophoblastic ischaemia and the outpouring of maternal catecholamines, leading to increased left ventricular afterload and increasing ventricular volumes, resulting in increased left ventricular stroke work and demand myocardial ischaemia. This is the substrate for ventricular arrhythmias. Foetal cardiac dysfunction is most likely on the basis of the increased afterload, consequent upon widespread vasoconstriction, due to angiogenic imbalances.

In this integrated model, chronic trophoblastic ischaemia is the central role player by releasing vasoactive substances that induce haemodynamic alterations in the materno-foetal complex, augmented and modified by 'latent' maternal cardiovascular dysfunction and increased maternal catecholamine secretion on the one hand, and altered foetal signalling mechanisms on the other, all three components of the materno-placental-foetal complex being in constant interaction with each other. This unified hypothesis may explain the development of both maternal and foetal morbidity and/or mortality on a unitary basis in severe, complicated pre-eclampsia.

Keywords: pre-eclampsia, maternal haemodynamics, foetal cardiaco haemodynamics, myocardial performance index, E/A ratio, foetal cardiac Doppler

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We present an integrated model of materno-foetal cardiac dysfunction, based on our studies on maternal and foetal haemodynamics, as well as other studies in the literature. Maternal cardiovascular deterioration in the mother in severe pre-eclampsia is due to a combination of factors, which may culminate in acute pulmonary oedema and cardiac failure. In the setting of severe trophoblastic ischaemia, the release of anti-angiogenic factors and an outpouring of maternal catecholamines leads to widespread elevation in systemic vascular resistance and endothelial cell damage, resulting in a sharp rise in left ventricular afterload and increasing ventricular volumes, which result in increased left ventricular stroke work and demand myocardial ischaemia. This is the substrate for the development of ventricular arrhythmias, in particular ventricular tachycardia.

These factors could lead to cardiac failure in severe pre-eclampsia, either in combination or independently of each other. This will depend on a number of variables, including the magnitude of the angiogenic imbalances with resultant elevation in systemic vascular resistance, the severity of changes in myocardial relaxation and diastolic filling, gene–environment interaction, and the presence of pre-existing latent cardiovascular dysfunction. The overall balance of these interactions could explain the different pathophysiological pathways that lead to the onset of cardiac failure if myocardial impairment predominates, or acute pulmonary oedema in severe pre-eclampsia when the afterload mismatch is acute and severe, with marked increases in diastolic filling pressures that transit to the pulmonary vasculature, which leads to pulmonary vasoconstriction.

In terms of foetal cardiac function, there has been corroboration, with similar conclusions reached by our studies and other related studies investigating foetal cardiac haemodynamics in intra-uterine growth restriction (IUGR) and pre-eclampsia, in that altered cardiac function was demonstrated, as evidenced by increased myocardial performance indices and altered transmitral E/A ratios. The E/A ratio is reflective of diastolic dysfunction, and similar to the adult haemodynamic changes in pre-eclampsia, significant diastolic dysfunction was also noted in foetuses in IUGR and pre-eclampsia. Cardiac dysfunction was also noted to worsen with worsening placental vascular resistance. In pre-eclampsia in particular, foetal cardiac dysfunction is most likely on the basis of the increased afterload consequent upon widespread vasoconstriction due to angiogenic imbalances.

It is generally accepted that pre-eclampsia is related to placental maladaptation. Poor trophoblastic invasion and utero-placental artery remodelling in pre-eclampsia increases reactive oxygen species (ROS), hypoxia and endothelial dysfunction. This defective trophoblastic invasion, with its resultant ischaemia, favours oxidative stress, consequent oxidative damage and inflammation. Within the trophoblastic cell, oxidative stress from unbalanced free radical formation is formed from different sources such as xanthine oxidase.
(XO), endothelial nitric oxide synthase (eNOS) uncoupling, NADPH oxidase and mitochondria. Ultimately the reunion of all these events leads to peroxynitrate formation, lipid peroxidation, protein modification, matrix metalloproteinase (MMP) activation and DNA damage, contributing to endothelial dysfunction.\textsuperscript{24,25} The source of the complex mediators is within the ischaemic trophoblastic cell, which filters into the maternal and foetal circulations.

One of the main mechanisms of endothelial dysfunction involves the release of soluble fms-like tyrosine kinase 1 (sFLT-1), an anti-angiogenic protein and inhibitor of vascular endothelial growth factor (VEGF) that works by enhancing the endothelial dysfunction already established by oxidative stress, ROS and damage.\textsuperscript{26} Immediately after placental reperfusion injury, re-established blood flow releases cytokines, TNF-\alpha, interleukin-6, interleukin-10, C-reactive protein and damaging levels of ROS such as superoxide in response to these events.\textsuperscript{27} These complex mediators and the constant interaction and interplay between the three components of pregnancy, that is, mother, foetus and placenta, lead to the unified hypothesis that may explain the development of both maternal and foetal morbidity and/or mortality on a unitary basis in severe, complicated pre-eclampsia.

Based on the data,\textsuperscript{1-27} a unified theory of cardiac dysfunction in pre-eclampsia in the materno-foetal complex could be proposed, on the basis that both the maternal and foetal compartments are exposed to similar haemodynamic challenges. Both maternal and foetal compartments are flooded with anti-angiogenic substrates and complex mediators from a chronically ischaemic placenta, causing widespread vasoconstriction and endothelial cell damage. This is augmented by substantial increases in catecholamine secretion in the maternal compartment, resulting in changes in maternal left ventricular filling and diastolic dysfunction, left ventricular hypertrophy; increasing end-systolic and end-diastolic left ventricular volumes and the precipitation of myocardial ischaemia and arrhythmias with cardiac decompensation. A similar pathophysiology in the foetus leads to diastolic dysfunction (altered E/A ratios) and altered global cardiac function (as reflected in abnormal myocardial performance indices). The response of the maternal component in the pregnancy state is further modified by pre-existing or subclinical, latent cardiovascular disease. These findings fit well into a tri-aetiological/pathophysiological basis for pre-eclampsia (Figs 1, 2):

- a maternal component from potential or pre-existing cardiovascular disease, showing up as superimposed severe pre-eclampsia (mother failing the cardiovascular stress of pregnancy)
- a placental component from chronic utero-placental ischaemia due to placental maladaptation and lack of placenta vascular transformation
- a foetal component, which induces compensatory signalling mechanisms in response to the chronic utero-placental ischaemia to improve placental circulation, and also exhibiting cardiac haemodynamic changes in itself.

This integrated model proposes a holistic approach in the evaluation of the cardiac status of the materno-foetal complex

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**Fig. 1.** Pathophysiologic pathway to cardiac dysfunction in the materno-foetal complex in severe pre-eclampsia, showing the proposed interaction of the materno-placental-foetal complex with each other. STMB: syncytiotrophoblast microparticles, AT1-AA: circulating auto-antibodies to angiotensin II AT-1 receptors, VEGF: vascular endothelial growth factor, PLGF: placental growth factor, sflt-1: soluble fms-like tyrosine kinase 1.

**Fig. 2.** Integrated algorithm for the development of acute pulmonary oedema in severe pre-eclampsia, and a proposed unified theory of cardiac dysfunction of the materno-foetal complex. SVR: systemic vascular resistance, LVH: left ventricular hypertrophy, LV: left ventricle, ESV: end-systolic volume, EDV: end-diastolic volume, MPI: myocardial performance index, BNP: brain natriuretic peptide.
using combined Doppler echocardiography (maternal and foetal), electrographic monitoring, and cardiac biomarkers such as brain natriuretic peptide to properly manage the complex obstetric syndrome of pre-eclampsia and its related phenotypes, in an attempt to detect early cardiovascular changes and reduce both maternal and foetal morbidity and mortality rates.

**Conclusion**

An integrated model of materno-foetal cardiac dysfunction in severe pre-eclampsia is presented, whereby chronic trophoblastic ischaemia is the central role player, releasing vasoactive substances that induce haemodynamic alterations in the materno-foetal complex. This scenario is augmented and modified by ‘latent’ maternal cardiovascular dysfunction and increased maternal catecholamine secretion on the one hand, and altered foetal signalling mechanisms on the other. All three components of the materno-placental-foetal complex are in interplay and in constant interaction with each other. This unified hypothesis may explain the development of both maternal and foetal morbidity and/or mortality on a unitary basis in severe, complicated pre-eclampsia. Maternal and foetal echocardiography should therefore be incorporated in the work-up of severe pre-eclampsia to risk-stratify these cases, in order to enable clinicians to choose the appropriate acute hypertensive drug therapy and plan optimal management pathways.

**References**