Potential Cell Signalling Mechanisms Involved in Differential Placental Angiogenesis in Mild and Severe Pre-Eclampsia

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Abstract

Fetal and neonatal morbidity and mortality is high in severe pre-eclampsia compared with mild pre-eclampsia and normotensive pregnancies. Causes for these fetal disturbances had been associated with iatrogenic prematurity and reduction in placental blood flow. Actual evidences suggest that in severe (early-onset) pre-eclampsia a reduction in placental angiogenesis could be a mechanism responsible for the reduced placental blood flow, while in mild (late-onset) pre-eclampsia normal placental blood flow could result from either no alteration or increased placental angiogenesis, or reduced vessel resistance. Since adenosine is involved in endothelium proliferation and angiogenesis, and umbilical and maternal blood level of this nucleoside is elevated in pre-eclampsia compared with normal pregnancies, it is feasible that placental angiogenesis in mild and/or severe pre-eclampsia involves adenosine-dependent cell signaling mechanisms. There are not reports regarding adenosine role in placental angiogenesis neither in normal nor in pathological pregnancies. However, it is well established that adenosine stimulates adenosine receptors triggering expression of angiogenic factors such as vascular endothelial growth factor (VEGF). VEGF stimulates VEGF receptors type 1 and 2, activating signaling cascades that involve increased synthesis of endothelial-derived nitric oxide (NO). On the other hand, the soluble VEGF receptor type 1 (sFlt-1), whose plasma concentration is increased in severe compared with mild pre-eclampsia, reduces angiogenesis, spotting sFlt-1 as a factor that could potentially be involved in this phenomenon. This review focuses on the available evidence regarding a potential differential mechanism of placental angiogenesis in mild compared with severe pre-eclampsia, and analyzes the potential role of adenosine/VEGF/VEGF receptors/NO signaling cascade in this phenomenon.