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Combining metformin and sulfasalazine additively reduces the secretion of antiangiogenic factors from the placenta: Implications for the treatment of preeclampsia

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ABSTRACT

Introduction: The antiangiogenic factors soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sENG) are elevated in preeclampsia and have been implicated in its pathogenesis. We have previously demonstrated metformin and sulfasalazine independently reduce antiangiogenic factor secretion. Here we examined whether combining metformin and sulfasalazine may be more effective than either alone in reducing placental expression and secretion of antiangiogenic and angiogenic factors and the expression of markers of endothelial dysfunction.
Methods: We performed functional experiments using primary human placenta to explore the effect of metformin and sulfasalazine, at lower doses than previously explored, individually and in combination, on sFlt-1 and sENG secretion and placental growth factor (PlGF) and vascular endothelial growth factor (VEGFα) expression. Using primary endothelial cells we induced dysfunction using cytokine tumor necrosis factor-α (TNF-α) and assessed the effect of low dose combination treatment on the expression of vascular cell adhesion molecule-1 (VCAM-1) and Endothelin-1 (a potent vasoconstrictor).
Results: We demonstrated combination metformin and sulfasalazine was additive in reducing sFlt-1 secretion from cytotrophoblasts and placental explants. Combination treatment was also additive in reducing sENG secretion from placental explants. Furthermore, combination treatment increased cytotrophoblast VEGFα mRNA expression. Whilst combination treatment increased PlGF mRNA expression this was similar to treatment with sulfasalazine alone. Combination therapy reduced TNFα induced endothelin-1 mRNA expression however did not change VCAM expression.
Discussion: Low dose combination metformin and sulfasalazine reduced cytotrophoblast sFlt-1 and sENG secretion, increased VEGFα expression and reduced TNFα induced endothelin-1 expression in primary endothelial cells. Combination therapy has potential to treat preeclampsia.

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