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Sulfasalazine reduces placental secretion of antiangiogenic factors, up-regulates the secretion of placental growth factor and rescues endothelial dysfunction

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ABSTRACT

Background: Preeclampsia is a major complication of pregnancy with no medical treatment. It is associated with placental oxidative stress, hypoxia and inflammation leading to soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sENG) secretion and reduced placental growth factor (PlGF). This results in widespread endothelial dysfunction causing hypertension and multisystem organ injury. Sulfasalazine is an anti-inflammatory and antioxidant medication used to treat autoimmune disease. Importantly, it is safe in pregnancy. We examined the potential of sulfasalazine to quench antiangiogenic factors and endothelial dysfunction and increase angiogenic factor secretion.

Methods: We performed functional experiments using primary human pregnancy tissues to examine the effects of sulfasalazine on sFlt-1, sENG and PlGF secretion. Sulfasalazine is known to inhibit nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB) and upregulate heme-oxygenase 1 (HO-1) thus we explored the effect of these transcription factors on sFlt-1 secretion from human cytotrophoblasts. We examined the ability of sulfasalazine to reduce key markers of endothelial dysfunction and dilate whole blood vessels.

Findings: We demonstrate sulfasalazine administration reduces sFlt-1 and sENG and upregulates PlGF secretion from human placental tissues. Furthermore sulfasalazine mitigates endothelial dysfunction in several *in vitro*/*ex vivo* assays. It enhanced endothelial cell migration and proliferation, promoted blood vessel dilation (vessels obtained from women at caesarean section) and angiogenic sprouting from whole blood vessel rings. The effect of sulfasalazine on the secretion of sFlt-1 was not mediated through either the NFkB or HO-1 pathways.

Interpretation: We conclude that sulfasalazine reduces sFlt-1 and sENG secretion and endothelial dysfunction and upregulates PlGF. Sulfasalazine has potential to treat or prevent preeclampsia and warrants investigation in clinical trials.

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