## **RESEARCH HIGHLIGHTS**

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## PRE-ECLAMPSIA

## sFLT1 inhibits NO signalling

Circulating levels of fms-like tyrosine kinase 1 (sFLT1) are elevated in patients with pre-eclampsia and correlate with adverse outcomes; however, the molecular mechanisms that underlie the pathological effects of sFLT1 are unclear. In a new study, Ananth Karumanchi and coworkers show that overexpression of sFlt1 in mice mimics human pre-eclampsia through inhibition of the nitric oxide (NO) signalling pathway.

"In this study, we demonstrate that sFLT1 induces endothelial dysfunction by impairing endothelial NO synthesis and promoting angiotensin II sensitivity, and that the FDA-approved drug sildenafil restores NO signalling and reverses sFLT1-induced hypertension and angiotensin II sensitivity," explains Karumanchi. "These data support the concept that endothelial dysfunction due to high circulating sFLT1 levels might be the primary event leading to enhanced vasoconstrictor sensitivity in pre-eclampsia."

The researchers showed that overexpression of sFlt1 was sufficient to inhibit endothelial NO synthase (NOS) phosphorylation, and induce hypertension, oxidative stress and vascular sensitivity to angiotensin II. Administration of the NOS inhibitor L-NAME to pregnant mice recapitulated the oxidative stress and angiotensin sensitivity induced by sFlt1 overexpression. Conversely, treatment with sildenafil — a phosphodiesterase 5 inhibitor that increases cGMP levels and enhances NO signalling — was sufficient to restore angiotensin II resistance and inhibit hypertension in sFlt1-overexpressing mice. "Importantly, the anti-hypertensive effects of sildenafil in our mouse model were associated with improved uterine blood flow. decreased uterine vascular resistance, and improved fetal weights, unlike current anti-hypertensive therapies used in pregnancy," says Karumanchi.

The researchers will now evaluate the role of other molecules altered in pre-eclampsia, such as soluble endoglin, in the pathogenesis of angiotensin II sensitivity and hypertension. They also plan to test the efficacy of sildenafil for the prevention of pre-eclampsia-related morbidity in pregnant women with early biomarker-based evidence of the disease. *Andrea Aguilar* 

ORIGINAL ARTICLE Burke, S. D. *et al.* Soluble fms-like tyrosine kinase 1 promotes angiotensin II sensitivity in preeclampsia. *J. Clin. Invest. <u>http://dx.doi.org/10.1172/ICl83918</u> (2016)*