Team finds key signaling pathway in cause of preeclampsia

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A team of researchers led by a Wayne State University School of Medicine associate professor of obstetrics and gynecology has published findings that provide novel insight into the cause of preeclampsia, the leading cause of maternal and infant death worldwide, a discovery that could lead to the development of new therapeutic treatments.

Nihar Nayak, D.V.M., Ph.D., is the principal investigator of the study, "Endometrial VEGF induces placental sFLT1 and leads to pregnancy complications," published Oct. 20 in the online version of *The Journal of Clinical Investigation*.

"Preeclampsia is a leading cause of maternal and fetal morbidity and mortality worldwide, yet its pathogenesis is still poorly understood," Nayak said. "Many studies have suggested that elevated circulating levels of sFlt1 (a tyrosine kinase protein that disables proteins essential to blood vessel growth) contribute to the maternal symptoms of vascular dysfunction that characterize preeclampsia, but the molecular underpinnings of sFlt1 upregulation in preeclampsia have so far been elusive. Our manuscript describes the novel, field-changing finding that vascular endothelial growth factor, or VEGF, of maternal origin can stimulate soluble sFlt1 production by the placenta and that this signaling is involved in the cause of preeclampsia."

Preeclampsia is a sudden increase in blood pressure after the 20th week of pregnancy. Indicated by a sudden increase in blood pressure and protein in the urine, preeclampsia warning signs, in addition to elevated blood pressure, can include headaches, swelling in the face and hands, blurred vision, chest pain and shortness of breath. While the condition can manifest within a few hours, some women report few or no symptoms.

The condition is responsible for 76,000 maternal deaths and more than 500,000 infant deaths every year, according to estimates from the Preeclampsia Foundation. It can affect the liver, kidney and brain. Some mothers develop seizures (eclampsia) and suffer intracranial hemorrhage, the main cause of death in those who develop the disorder. Some women develop blindness. The babies of preeclamptic mothers are affected by the condition and may develop intrauterine growth restriction or die in utero.

Many experts believe preeclampsia results from insufficient blood supply to the uterus and placenta, causing the development of high blood pressure. The increase in maternal blood pressure is a compensatory response to improve the condition of the fetus. Preeclampsia may have evolved to protect the infant, but when the disease is out of control it threatens the health of the mother. The earlier the disease starts in pregnancy, the worse the outcome can be for the baby and mother. Women with preeclampsia often do not feel effects until the condition is severe and becomes life-threatening. Effects on the mother include cardiac problems, possible brain hemorrhage, acute renal failure, blood clotting problems and possible blindness. If left undetected, the condition can progress to eclampsia and the mother may begin convulsing. For the fetus, preeclampsia has been connected to a reduction in placental blood flow, resulting in physical and mental disability, the slowing of fetal development, and in severe cases, infants may be stillborn.

While VEGF is essential for normal embryonic development, Nayak said, his team's research has demonstrated that even mild elevation of VEGF levels during early pregnancy can cause severe placental vascular damage and embryonic lethality. The results show that modest increases in VEGF could also be a primary trigger for elevation of placental sFlt1 expression, leading to preeclampsia.

Furthermore, the findings indicate that sFLT1 plays an essential role in maintaining vascular integrity in

the placenta in later stages of pregnancy and suggest that overproduction of sFlt1 in preeclampsia, although damaging to the mother, serves a critical protective function for the placenta and fetus by "sequestering" excess maternal VEGF.

According to the Preeclampsia Foundation, the condition, also known as toxemia or pregnancy-induced hypertension, affects 5 percent to 8 percent of pregnancies. Left untreated or undetected, preeclampsia can rapidly lead to eclampsia, one of the top five causes of maternal death and infant illness and death. Approximately 13 percent of all maternal deaths worldwide – the death of a mother every 12 minutes – have been attributed to eclampsia. The foundation reports that preeclampsia is responsible for nearly 18 percent of all maternal deaths in the United States.

Even if treated successfully, preeclampsia can bring future health problems for mothers. Women who have had preeclampsia have double the risk for heart disease and stroke over the next five to 15 years after they are treated.

More information: Endometrial VEGF induces placental sFLT1 and leads to pregnancy complications, *J Clin Invest*. DOI: 10.1172/JCI76864

sFLT1 in preeclampsia: trophoblast defense against a decidual VEGFA barrage? *J Clin Invest*. DOI: 10.1172/JCI78532

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