New risk factor identified for high blood pressure during pregnancy

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Preeclampsia is a serious complication of pregnancy and the major cause of death for both mother and child in Europe and the U.S. It affects about one in 20 pregnancies. The main symptoms are high blood pressure and protein in the urine. The cause of preeclampsia is still unclear. Dr. Florian Herse (Experimental and Clinical Research Center (ECRC) of the Max Delbrück Center (MDC) and the Charité), Dr. Ralf Dechend (ECRC and Helios Klinikum Berlin-Buch) and their collaborators have now identified an enzyme that is overexpressed in affected women and thus apparently contributes to development of the condition. In animal experiments, the researchers inhibited this enzyme and were able to ameliorate the disease process.

Preeclampsia originates in the placenta, which supplies the embryo/fetus in the womb with nutrients. For their study, Dr. Herse, numerous contributors, and Dr. Dechend analyzed tissue samples from 25 women diagnosed with preeclampsia and from 23 healthy pregnant women as controls. The tissue samples of the preeclamptic women were obtained from hospitals in Finland, Norway, Austria, and the U.S. that cooperated closely in the study.

Using gene-chip technology, the researchers in Berlin analyzed the expression of almost 40,000 genes. They found that in women with preeclampsia, levels of the CYP2J2 enzyme were unusually high in placental cells and the uterine lining (decidua). The placenta consists of fetal cells; the decidua, by contrast, is solely maternal tissue. The enzyme is involved in the production of specific metabolites called EETs

(epoxyeicosatrienoic acids) which, among other things, regulate inflammatory processes, vascular growth, and blood pressure.

Dr. Herse and team succeeded in identifying the cells that produce the CYP2J2 enzyme as trophoblasts, which fulfill an important function in pregnancy. These fetal cells migrate from the placenta into the maternal decidua. Trophoblasts are key contributors to spiral-artery remodeling and thus ensure that the fetus is sufficiently supplied with nutrients. However, if the trophoblasts do not grow deeply enough into the decidua, this remodeling process is disturbed. As a consequence, the fetus cannot be sufficiently supplied with nutrients, leading to preeclampsia. EETs evidently have a harmful effect because they activate a substance which prevents the trophoblasts from growing into the decidua.

Both a protective and damaging effect

Previous studies indicated that EETs exert only positive effects on the cardiovascular system. EETs generally mediate vascular expansion and reduce blood pressure. They also protect the tissue from dying of oxygen deficiency. In normal pregnancies EET levels are slightly elevated.

Previous experiments with healthy pregnant rats showed that pharmacological inhibition of the CYP2J2 enzyme and the associated inhibition of EET production lead to hypertension and kidney failure. In pregnant rats with preeclamptic symptoms, however, opposite effects may occur. By inhibiting CYP2J2, the ECRC researchers were able to lower blood pressure levels in these animals.

How did these conflicting observations come about? Dr. Herse and team demonstrated that the EETs can be converted into other metabolites. A specific enzyme (cyclooxygenase, COX) alters these components further in such a way that they cause vasoconstriction and thus an increase in

blood pressure. EETs that normally lower blood pressure can evidently produce metabolites that cause blood pressure to rise in preeclampsia. If however the researchers inhibited the cyclooxygenase in the pregnant animals, the EETs were not converted further and the blood pressure did not increase. "This work shows that the increased production of EET in the placenta and the conversion via cyclooxygenase into hormones that increase blood pressure both favor the development of preeclampsia," Dr. Herse and Dr. Dechend explained.

Messenger substance of the immune system apparently promotes the development of preeclampsia

But why do the bodies of women with preeclampsia produce more CYP2J2 and thus more EET? Tumor necrosis factor-alpha (TNF-alpha), a chemical messenger of the immune system, could possibly contribute. This signaling substance is released at early stages of pregnancy whenever placental blood flow is too low, causing oxygen deficiency. As the researchers showed, TNF-alpha promotes the production of CYP2J2 and EET in the placenta. In other tissues, this reaction would be useful, since EET rescues tissue from dying that has an insufficient supply of blood and therefore of oxygen. In the placenta, by contrast, this boost in production of CYP2J2 and EET could lead to a vicious circle. The trophoblasts do not grow as well into the decidua and the blood vessels and are not remodeled correctly, so that blood flow through the placenta and blood supply to the fetus deteriorates. As a consequence, the mothers becomes hypertensive and EETs under these conditions is converted in such a way that the blood pressure continues to increase.

Treatment of preeclampsia, which according to estimates costs many thousands of maternal lives across the globe every year, remains difficult. The only possibility is to induce delivery at an early stage if the clinical presentation is severe. In Germany, preeclampsia is the cause for

up to 20,000 premature births annually. Once the child is born, the symptoms subside in the mother. Nevertheless, she may suffer long-term increased risk for cardiovascular disease and develop heart attack, stroke, or hypertension at an early age. For the child, depending on the stage of fetal development, the premature birth may result in death or severe lifelong disability, and the child may also have an increased risk for cardiovascular disease later on. The research conducted by Dr. Herse, the entire team, and Dr. Dechend implicates a previously unknown mechanism. Their discovery may contribute to a better understanding of the disease process and its causes, and may ultimately aid in developing a therapy.

More information: CYP2J2 expression and circulating epoxyeicosatrienoic metabolites in preeclampsia, DOI: 10.1161/CIRCULATIONAHA.112.127340

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