Researchers report advances vs. preeclampsia, including potential prediction

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In as many as 8 percent of pregnancies worldwide, women who seem fine for months develop preeclampsia, a serious complication causing symptoms including high blood pressure, severe swelling, and problems with placental development. The untreatable and unpredictable condition, with no known cause, often requires premature delivery, and can sometimes kill the mother and the fetus.

In a new study, researchers led by a team at Brown University and Women & Infants Hospital describe two major advances: a well-defined animal model of preeclampsia and a potential lab test for diagnosing the disease in people.

"Our model is the first pregnancy-specific animal model," said Surendra Sharma, professor of pediatrics at the Warren Alpert Medical School of Brown University and a research scientist at Women & Infants, "and our predictive assay is the first one where we can go back to the first trimester and predict problems."

Sharma is a senior author on the study, published online this month in *The American Journal of Pathology*. In addition to pediatrics researchers, the study also involved scientists at the Lifespan Center for International Health Research, Harvard Medical School in Boston, and Linkoping University and Helsingborg Hospital in Sweden.

Model mice

Building on research linking the presence of the immune system secretion Interleukin-10 (IL-10) to a successful course of pregnancy, the researchers started experimenting with mice genetically engineered to lack IL-10. They hypothesized that if they isolated blood serum from human patients with preeclampsia and gave a dose of it to the mice, the rodents would develop preeclampsia symptoms. That is exactly what happened.

Just to be sure, the researchers gave the preeclampsia serum to mice that were not pregnant. Nothing happened, confirming that the onset of preeclampsia symptoms in the engineered mice was a consequence of their pregnancy. Meanwhile, the researchers gave the preeclampsia serum to wild mice who were pregnant and found that they did not experience all the preeclampsia symptoms of mice without IL-10. That confirmed that pregnant mice lacking IL-10 provide a unique and dependable model of the disease.

The significance of having an animal model for preeclampsia is that it will allow for experiments that can shed light on the cause of the disease and its progression, Sharma said. That has already occurred in his research. For example, the team was able to observe something in the mice that is also observed in human preeclampsia patients: a disruption in the development of "spiral arteries," which bring nutrients to the fetus from the placenta.

Toward a diagnostic lab test

After observing how preeclampsia serum caused disruption to the spiral arteries, the team reasoned that preeclampsia serum might also disrupt the formation of vasculature in the lab. They created an in vitro culture of two key cell types involved in spiral artery development — endothelial cells and trophoblasts — and then exposed some to serum from women with normal pregnancies and some to preeclampsia serum

from women taken at various stages of their pregnancies.

The researchers found that vasculature developed normally in the presence of serum from women with normal pregnancies. But they also found that preeclampsia serum taken from women as early as 12 to 14 weeks into their pregnancies, about 10 to 12 weeks before they were diagnosed with preeclampsia, was able to disrupt vascular formation.

Sharma has filed a patent application for the test and has continued to refine it for eventual clinical use, a process that will require FDA approval.

"The idea is that we can predict preeclampsia ahead of time and women can be treated," Sharma said. Researchers, for example, are looking at dysregulated proteins in preeclampsia serum for their causative effects and as one avenue of managing preeclampsia. The idea is that normal counterparts of these proteins will rescue normal pregnancy and protect against the onset of preeclampsia disease. "Hopefully, hopefully preeclampsia can be controlled," Sharma said.

Provided by Brown University