

Pilot study suggests new approach to treat preeclampsia

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A novel therapy that reduces elevated blood levels of a potentially toxic protein in women with preeclampsia, a dangerous complication of pregnancy, may someday address the therapeutic dilemma posed by the condition – balancing life-threatening risks to the mother with the dangers that early delivery poses to an immature fetus. In a paper receiving online release in the journal *Circulation*, a team of U.S. and German researchers report promising results from their pilot study of a filtration technology that reduces reduce excess blood levels of soluble Flt-1, a protein that limits the growth of blood vessels, in women with very preterm preeclampsia.

"Introducing new therapies in pregnancy is uncommon because of the need to avoid extra risks to both the mother and baby," says Ravi Thadhani, MD, MPH, of the Massachusetts General Hospital (MGH) Division of Nephrology, co-corresponding author of the report. "In this paper we show that a disease that affects thousands of women around the world may one day be able to be managed by the therapy we developed. This was a small, proof-of-concept study to see if the therapy is safe and possibly effective; so larger, randomized trials now need to be done."

Affecting 5 to 7 percent of pregnancies, preeclampsia is characterized by high blood pressure, protein in the urine and additional metabolic abnormalities. If symptoms progress, it can lead to kidney or liver failure, brain swelling, seizures and death. Since the only way to halt the process is to deliver the fetus, the earlier in a pregnancy preeclampsia occurs the greater the risk to the baby. Very preterm delivery – before



32 weeks of gestation – has been estimated to increase infant mortality as much as 70 times over full-term delivery at 37 or more weeks. Very preterm babies who do survive may face lifelong complications such as cerebral palsy, so finding an intervention that can safely prolong pregnancy is vitally important.

The underlying cause of preeclampsia is still unknown, but one hypothesis is that factors released into the bloodstream by the placenta damage blood vessels throughout the body. In a 2003 study Ananth Karumanchi, MBBS, of the Beth Israel-Deaconess Medical Center, a coauthor of the current study, identified soluble Flt-1 (FMS-like tyrosine kinase 1) as a possible factor in preeclampsia. Released by the placenta and other tissues, soluble Flt-1 blocks the vascular growth factor VEGF, which is essential to maintaining healthy blood vessels; and levels of soluble Flt-1 are extremely elevated in women with very preterm preeclampsia. Developing a preeclampsia treatment based on removing a factor like soluble Flt-1 rather than giving a drug that may have side effects of its own presented an attractive strategy.

Thadhani and his colleagues adapted the blood-filtering technologies used in apheresis to develop a method of rapidly removing soluble Flt-1 from the bloodstream. Since a blood test to measure soluble Flt-1 levels is available in Germany, Thadhani collaborated with Thomas Benzing, MD, University of Cologne, co-corresponding author of the *Circulation* paper, and Holger Stepan, MD, of University Hospital Leipzig, on the pilot clinical study. The first phase was designed to confirm the safety of the treatment and determine whether how long it was administered affected how much soluble Flt-1 was reduced. In five patients with very preterm preeclampsia and elevated soluble Flt-1, levels did drop in response to a single treatment, with a greater decrease associated with longer treatment. There were no major side effects, but because the treatment sessions were brief, no extension of pregnancy was expected or seen.



The researchers then offered three women with very preterm preeclampsia – from 27 to 30 weeks – the opportunity to receive several treatment sessions in an attempt to extend their pregnancies. Two patients, one of them carrying twins, received two treatments; and the third received four. After each treatment session, the patients' soluble Flt-1 levels dropped from 20 to 30 percent for several days and urinary protein levels also dropped. Various factors, including recurrence of preeclampsia symptoms, eventually required premature delivery of the babies; but the pregnancies had been maintained from two to three weeks after hospital admission. A comparison group of patients that received standard monitoring required delivery an average of 3.6 days after admission. While the babies of women receiving the novel treatment needed the type of support typically required for premature infants, they all were discharged from the hospital with few complications.

"There has never been an effective therapy for this condition," says Thadhani, an associate professor of Medicine at Harvard Medical School. "We've been working for over a decade to find ways to extend the baby's time in utero while preventing the rapid acceleration of preeclampsia that can take a mother from feeling fine to a coma in a matter of hours. One of the beauties of an approach based on removing something instead of giving a drug is that it can be carefully controlled and, if necessary, quickly turned off. While this study is too small to allow us to say that our treatment was responsible for extending these patients' pregnancies – that will require a larger, randomized clinical trial – this first step holds promise."

Provided by Massachusetts General Hospital

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