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Tracing the molecular causes of preeclampsia

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Preeclampsia is one of the most dangerous conditions for the expectant mother and the unborn child and is characterized by elevated blood pressure and protein in the urine in the last trimester of pregnancy. The cause for this life-threatening disease has long remained elusive. Recently however, Dr. Ananth Karumanchi (Associate Professor of Medicine, Beth Israel Deaconess Medical Center & Harvard Medical School, Boston, Massachusetts, USA) has identified a new molecular pathway that leads to preeclampsia in humans and thus creating new avenues for the development of a therapy, he reported at the 1st ECRC "Franz-Volhard" Symposium on September 8, 2012 at the Max Delbrück Center for Molecular Medicine (MDC) Berlin-Buch.

"Preeclampsia is among the three diseases that cause death amongst mothers, their unborn and newly born babies, accounting for nearly 70,000 maternal deaths a year worldwide," Dr. Karumanchi pointed out in Berlin. The other two are severe bleeding and infection. Researchers suspect that the number of deaths caused by preeclampsia is underreported and is actually much higher. "Preeclampsia is especially lethal in the underdeveloped world where medical care and facilities for emergencies and for caring for premature babies are lacking," Dr. Karumanchi said. Therefore, the death rate among those newborns is clearly higher than in countries with better medical care.

However, preeclampsia is a serious problem in industrialized countries, too. In Germany, for example, every year more than 20,000 babies are born prematurely due to preeclampsia. "In fact preeclampsia is among the leading causes of prematurely born babies," Dr. Karumanchi

stressed. As each additional week in the uterus of the mother lowers fetal morbidity and mortality, physicians strive to prolong pregnancy without compromising the safety of the mother.

If the condition becomes too dangerous for the pregnant woman, they intervene and induce labor. As soon as the child is born, the mother's symptoms disappear. But later in life the mothers can develop heart disease, hypertension and thyroid disorders due to preeclampsia. And premature babies run the risk, if they survive, of life-long disability.

Findings on molecular causes open up avenues for early diagnosis as well as therapy

Dr. Karumanchi was able to show that the placenta, the organ in the uterus which nourishes the embryo and the fetus, plays an important role in the onset of preeclampsia. It releases two different proteins. One of the proteins, the PlGF (placental growth factor) makes blood vessels grow towards the placenta. It is an angiogenisis factor which is part of the VEGF family, a large group of proteins that induces blood vessel growth. The antagonist to PlGF is sFlt-1 (soluble fms-like tyrosine kinase-1). It binds to PlGF and inhibits blood vessel growth. The levels of these two proteins in the blood of the pregnant women must be in balance for mother and unborn baby to stay healthy.

Dr. Karumanchi's team discovered that pregnant women with preeclampsia have too much sFlt-1 circulating in their blood, and too little PlGF. As a result the placenta is no longer well supplied with blood, and the fetus does not get enough nutrients. Also, lack of PlGF constricts the blood vessels, and the expectant mother's blood pressure becomes elevated – the main symptom of preeclampsia. As the kidneys are affected, too, the patient develops proteinuria, characterized by too much protein in the urine.

Whereas formerly preeclampsia in pregnant women could only be diagnosed by these symptoms – hypertension and proteinuria – the findings of Dr. Karumanchi now make it possible to detect preeclampsia at a very early stage, even before the first symptoms appear. Researchers and clinicians measure sFlt-1 and PlGF levels and they can determine if sFLT-1 levels are too high. They can then monitor the expectant mothers at a very early stage and help prevent the disease from progressing in order to avoid seizures and liver failure.

Dr. Karumanchi's research has already led to the first step to treat the disease through extracorporeal removal of excessive sFLT-1 from the blood. In a pilot study, Professor Ravi Thadhani (a colleague of his at Harvard Medical School) working with nephrologists and obstetricians in Germany (Cologne and Leipzig), showed last year that a single treatment of five pregnant women with preeclampsia lowered elevated levels of sFLt-1 in the blood. Repeated treatment of three additional patients with preeclampsia in the early onset of pregnancy (28, 27, 30 weeks of pregnancy) could reduce not only sFlt-1 but also proteinuria and stabilize blood pressure without apparent adverse events to either mother or fetus. In addition, the obstetricians were able to prolong pregnancy duration thus allowing the delivery of healthier babies. Dr. Karumanchi stressed that further studies are necessary to determine whether this intervention safely and effectively prolongs pregnancy and improves the condition of mother and child.

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