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Study yields potential drug targets for preeclampsia patients

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Preeclampsia, the most common complication of pregnancy, is a major cause of premature delivery and both maternal and fetal death, yet what causes the syndrome remains unclear. A new study indicates that molecules that send detrimental signals are abundant in certain tissues in preeclampsia patients. The study also documented some of the complications experienced by babies born to mothers with preeclampsia.

"Preeclampsia is a multifaceted complication found uniquely in the pregnant patient and one that has puzzled scientists for years," says the leader of the study, Mohammad N. Uddin, a research scientist and assistant professor in the obstetrics and gynecology department of the Scott & White Healthcare/Texas A&M Health Science Center College of Medicine in Temple, Texas.

Preeclampsia affects about 5 percent of expectant moms, usually in the second half of pregnancy. "By conservative estimates, these disorders are responsible for 76,000 maternal and 500,000 infant deaths each year" around the world, according to the Preeclampsia Foundation. Preeclampsia's hallmarks are high blood pressure and an overload of protein in the urine. Treatment options are limited, but the syndrome eventually goes away after birth.

During pregnancy, the placenta functions like a trading post of sorts: Inside the pancake-shaped organ, maternal and fetal blood is trucked through, nutrients and oxygen are delivered to the developing fetus, and waste products are shipped out for disposal. All of that life-sustaining

traffic requires a multitude of molecular signals, and Uddin's study zeroed in on the bad signals that may be involved in preeclampsia.

Uddin's team compared protein expression in samples from placentas and umbilical cords of 10 women who had experienced preeclampsia and 10 who had not. (The researchers also conducted the same analysis with rats.) They found that proteins that signal both cell stress and cell death were significantly higher in samples taken from the women who had experienced preeclampsia, Uddin says.

"Stress and (programmed cell death) signaling was upregulated in preeclamptic placentas and umbilical cords compared with normal pregnancies," Uddin says. In fact, the ratio of molecules Bax/Bcl-2, which is involved in programmed cell death, was increased 1.4-fold. Meanwhile the molecule Cox-2, which is related to inflammation, and the enzyme p38 MAPK, which is related to cell stress, were increased 2.5-fold and 3.0-fold, respectively.

The researchers say that the increase in those factors could reduce nutrient transport and send bad signals to the maternal vascular system, which circulates blood. In addition, Uddin says, these circulating factors may pass the placental barrier: "The fetus has to adapt to this impending intrauterine environment and detrimental signaling, and this adaptation increases the risk of disease happening later in life."

In addition to analyzing what molecules were more pronounced in preeclampsia, the researchers were interested in learning more about the effects of the syndrome on study participants' babies. They found that the average hospital stay for preeclampsia babies was significantly longer: Those newborns stayed six days on average, while the babies born to mothers without preeclampsia stayed a little over three days on average.

While there were no complications reported for the babies from normal pregnancies, the babies with preeclamptic moms had a slew of issues: One had low blood sugar; four had jaundice; three had respiratory distress syndrome; one had extra and fused digits; one was overdue; one had abnormal abdominal fluid accumulation; and one had intrauterine growth restriction.

Uddin noted that there are numerous well-known effects of preeclampsia on babies: "These long-term effects are increased risks of hypertension and type 2 diabetes mellitus, aortic wall thickening (an early marker of atherosclerosis in children), increased risk of stroke, intellectual disabilities, hearing disabilities, neurodevelopmental delay, cerebral palsy and an increased risk of metabolic disorders."

Uddin says that the team's identification of the molecules overexpressed in the tissues from preeclampsia patients raises the possibility that those signals could be therapeutically blocked one day.

More information: Mohammad N. Uddin presented the team's findings during the Experimental Biology 2014 meeting on Monday, April 28, at the Cell Signaling poster session in Exhibit Halls A-D (Poster #D324), San Diego Convention Center.

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