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Key to pre-eclampsia may be found in misfolded proteins in the urine

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Clues to the cause of preeclampsia, a common, but serious hypertension complication of pregnancy that has puzzled doctors and researchers for decades, point to proteins that misfold and aggregate, according to Yale School of Medicine researchers.

These misshapen proteins can be easily detected in the urine, affording a new approach to early diagnosis of the disease, the Yale researchers report in new findings presented at the Society for Maternal Fetal Medicine scientific meetings in San Diego, Calif.

Preeclampsia is one of the most common causes of death in pregnant women in the United States and is responsible for about 76,000 maternal deaths worldwide each year. It is also a leading cause of preterm delivery. Delivery is the only reliable treatment for preeclampsia, and establishing a correct diagnosis can be difficult, especially in women with preexisting hypertension, lupus or kidney disease.

"These results support the hypothesis that preeclampsia is a pregnancy-specific protein misfolding disease," said lead author on the abstract, Irina Buhimschi, M.D., associate professor in the Department of Obstetrics, Gynecology & Reproductive Sciences. "Our urine dye test is a rapid and non-invasive test that can be used to definitively diagnose preeclampsia."

In a study of 111 pregnant women, Buhimschi and her team used proteomics to identify key abnormal proteins in the urine weeks before

preeclampsia becomes clinically apparent. In order to carry out their individual functions properly, proteins must fold themselves correctly into three-dimensional structures. Misfolding, or failure to fold into the intended shape, produces proteins with different properties that are mainly guided by their shape rather than their amino acid sequence. Proteins of different amino acid sequences may share common shapes when misfolded.

Buhimschi and her team designed a test based on a dye that sticks to misfolded proteins. They analyzed the urine of women in the study starting in the first trimester of pregnancy. Buhimschi was able to use this simple test to identify a study participant who went on to develop severe preeclampsia and required early delivery.

Further work in Buhimschi's lab, using conformation-specific antibodies developed in Charles Glabe's laboratory at University of California-Irvine, showed that misfolded shapes similar to those found in Alzheimer's disease are also present in the urine of preeclamptic women. In contrast to the misfolded proteins identified in Alzheimer's disease, however, the misfolded aggregates identified in preeclampsia are composed of a group of different proteins, including SERPIN-A1 (also known as alpha-1-antitrypsin).

"Our findings are compelling for several reasons," said Buhimschi. "This novel identification of preeclampsia as a disorder of protein misfolding opens a door for researchers that may lead to testing of new drugs or developing new therapies. Our future work will seek to determine whether the different shapes employed by the misfolded proteins in preeclampsia are linked to specific clinical symptoms and the different ways this intriguing disease manifests."

Source: Yale University