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Biomarker Discovery May Lead to Reliable Blood Test for Ectopic Pregnancy

Scientists at The Wistar Institute and the University of Pennsylvania School of Medicine report the discovery of protein markers that could provide physicians with the first reliable blood test to predict ectopic pregnancies. Their findings are presented in the February 16 issue of the Journal of Proteome Research, currently available online. In a related small-scale study of clinical samples, published recently in the journal Fertility and Sterility, the researchers found that one of the proteins -- ADAM12 -- showed a nearly 97 percent correlation with ectopic pregnancy.

Ectopic pregnancies occur when a fertilized embryo fails to implant in the womb, often getting caught in the Fallopian tubes. As the embryo grows, the tube could rupture, which results in the loss of the embryo and threatens the life of the pregnant woman. Ectopic pregnancies occur in about one in 40 to 100 pregnancies, and it is a leading cause of death in the first trimester of pregnancy. There is no single proven blood test for ectopic pregnancy, and current diagnosis relies on the use of ultrasound.

"Here we describe a group of proteins that, with further refinement, could make a simple blood test for ectopic pregnancy," said David W. Speicher, Ph.D., Professor and co-leader of Wistar's Molecular and Cellular Oncogenesis Program and Director of Wistar's Center for Systems and Computational Biology. "This is also a proof-of-principle demonstration of a new method for the discovery of new blood-borne markers that may serve as diagnostic blood tests to detect or predict a variety of clinical conditions and diseases, from ectopic pregnancy to cancer."

According to Speicher, their study points to the power of proteomics -- the study of the sum total of proteins that the body is making at a given time -- in understanding the state of health or disease in people. Proteomics provides researchers an "unbiased" approach to the discovery of biomarkers, proteins in this case, which could be used to signal the presence of a particular clinical disorder or disease.

"Most biomarkers being used clinically today were first discovered by focused studies of proteins known to be associated with a disease, such as the prostate-specific antigen, PSA, test for prostate cancer," Speicher explained. "Proteomics is unbiased in the sense that we are not trying to confirm the presence of a known protein, we simply compare the entire protein profile of people in a particular clinical condition or disease state to the protein profile of people in a healthy state."

"Instead of a single biomarker, we can define a panel of such markers, creating a test that weighs the relative importance of individual proteins," Speicher said. "It makes for more sensitive, reliable tests."

In the present study, the Speicher laboratory compared the proteomic signature of blood samples taken from known cases of ectopic pregnancy with blood samples taken from women who experienced a normal pregnancy. They discovered about 70 candidate biomarkers that could signal ectopic pregnancy, which stringent statistical analysis whittled down to the 12 most promising biomarkers. While some of the proteins had previously known associations with ectopic pregnancies, the researchers found at least two, including ADAM12, which had never been previously associated with ectopic pregnancy.

Speicher and his team worked in collaboration with Kurt T. Barnhart, M.D., a Professor of Obstetrics and Gynecology at the University of Pennsylvania School of Medicine. In a

study recently published online by the Journal Fertility and Sterility, Barnhart, Speicher and colleagues at Penn and two other urban academic medical centers reported on elevated ADAM12 levels in women seen in emergency rooms for bleeding resulting from an undiagnosed ectopic pregnancy.

The next step is to further confirm and validate the usefulness of their panel of biomarkers using additional patient samples in order to create a practical, reliable blood test for ectopic pregnancy, Speicher says. Among their goals is to identify particular isoforms -- that is, variations of a given protein -- that are most relevant to identifying ectopic pregnancy. Many proteins exhibit different isoforms in the body; that is, proteins that come from related genes, differences in processing the gene or modification of the protein in some way by cellular processes.

"The great power of biomarkers is to detect clinical disorders such as ectopic pregnancy or diseases, such as

cancer, early when it is often easiest to treat the patient," Speicher said. "Here we can envision a useful blood test that could, as part of routine early prenatal care, save the lives of many women."

Funding for this study was provided through grants from the National Institutes of Health and the Philadelphia Health Care Trust. The lead author of the study is Lynn A. Beer, a research assistant in the Speicher laboratory. Co-authors also include Hsin-Yao Tang, Ph.D., a Wistar staff scientist, and Sira Sriswasdi, a Penn graduate student, both of whom are also members of the Speicher laboratory.

Source: Lynn A. Beer, Hsin-Yao Tang, Sira Sriswasdi, Kurt T. Barnhart, David W. Speicher. Systematic Discovery of Ectopic Pregnancy Serum Biomarkers Using 3-D Protein Profiling Coupled with Label-free Quantitation. *Journal of Proteome Research*, 2011; : 110107134921035 DOI: 10.1021/pr1008866