Research teams find biomarkers that predict common, severe pregnancy complication

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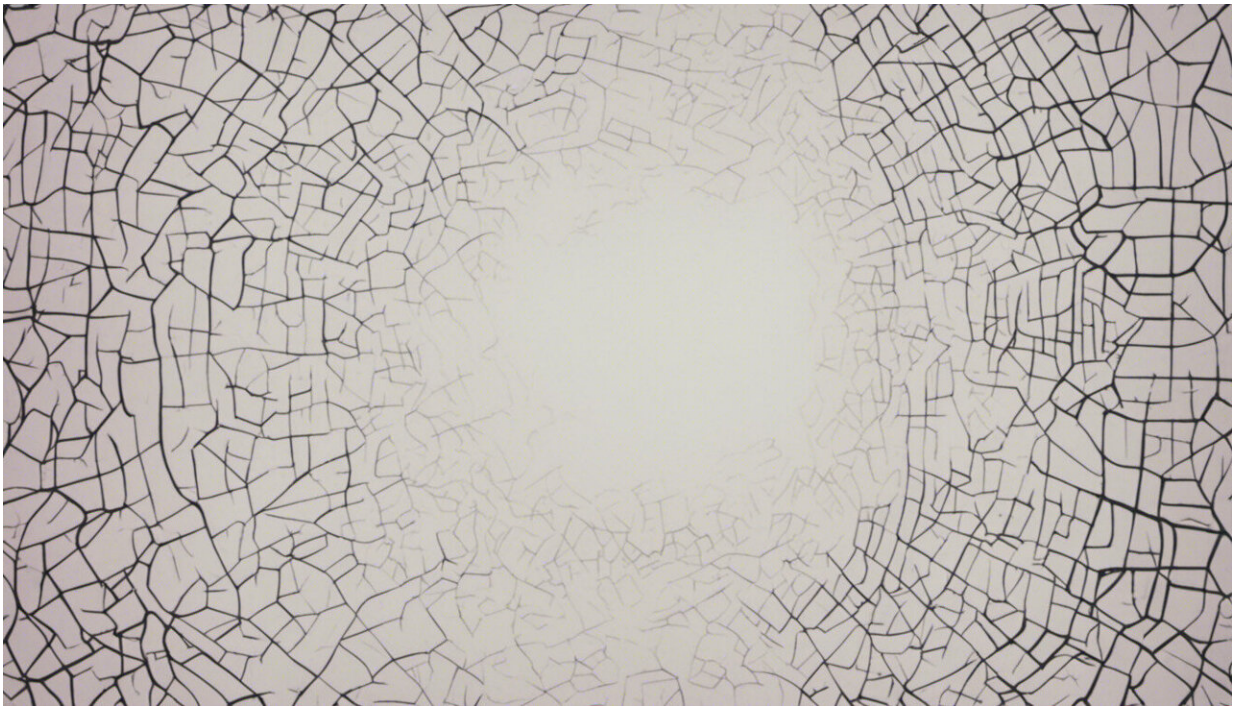

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A discovery by Stanford School of Medicine researchers of biomarkers in the blood and urine of women with a dangerous complication of pregnancy could lead to a low-cost test to predict the condition.

The findings, which published online Dec. 9 in *Patterns*, lay the

groundwork for predicting preeclampsia—one of the top three causes of maternal death worldwide—months before a pregnant woman shows symptoms. Predictive testing would enable better pregnancy monitoring and the development of more effective treatments.

Preeclampsia is characterized by high blood pressure late in pregnancy. It affects 3% to 5% of pregnancies in the United States and up to 8% of pregnancies worldwide, and it can lead to eclampsia, an obstetric emergency linked to seizures, strokes, permanent organ damage and death. At present, preeclampsia can be diagnosed only in the second half of pregnancy, and the sole treatment is to deliver the baby, putting infants at risk from premature birth.

"The advantage of predicting early in pregnancy who will get preeclampsia is that we could follow moms more closely for early symptoms," said the study's co-lead author, Ivana Marić, Ph.D., a senior research scientist in pediatrics at Stanford Medicine. In addition, taking low-dose aspirin starting early in pregnancy may lower preeclampsia rates in women at risk for the condition, but pinpointing who could benefit has been challenging, Marić said.

"There is really a need to identify those pregnancies to prevent tragic outcomes for mothers, and preterm births for babies, which can be very dangerous."

Marić shares lead authorship of the study with Kévin Contrepois, Ph.D., former scientific director of the Stanford Medicine Metabolic Health Center. The study's senior authors are Nima Aghaeepour, Ph.D., associate professor of pediatrics and of anesthesiology, perioperative and pain medicine; Brice Gaudilliere, MD, Ph.D., associate professor of anesthesiology, perioperative and pain medicine; and David Stevenson, MD, professor of pediatrics and director of the Stanford Prematurity Research Center, which supported the research.

"When you reduce preeclampsia, you also likely reduce preterm birth," Stevenson said. "It's a double whammy of good impacts."

To figure out which biological signals could provide an early warning system for preeclampsia, the Stanford Medicine research team collected biological samples from pregnant women who did and did not develop preeclampsia. They conducted highly detailed analyses of all the samples, measuring changes in as many biological signals as possible, then zeroing in on a small set of the most useful predictive signals.

"We used a number of cutting-edge technologies on Stanford University's campus to analyze preeclampsia at an unprecedented level of biological detail," Aghaeepour said. "We learned that a urine test fairly early on during pregnancy has a strong statistical power for predicting preeclampsia."

Measuring everything that changes in pregnancy

The research team collected biological samples at two or three points in pregnancy (early, mid and late) in 49 women, of whom 29 developed preeclampsia during their pregnancies and 20 did not. The participants were selected from a larger cohort of women who had donated biological samples for pregnancy research at Stanford Medicine.

For each time point, the participants gave blood, urine and vaginal swab samples. The samples were used to measure six types of biological signals: all cell-free RNA in blood plasma, a measure of which genes are active; all proteins in plasma; all metabolic products in plasma; all metabolic products in urine; all fat-like molecules in plasma; and all microbes/bacteria in vaginal swabs. The scientists also conducted measurements of all immune cells in plasma in a subset of 19 of the participants.

Using the resulting thousands of measurements, as well as information about which participants developed preeclampsia and when in pregnancy each sample was collected, the scientists used machine learning to determine which biological signals best predicted who progressed to preeclampsia.

They aimed to identify a small set of signals detectable in the first 16 weeks of pregnancy that could form the basis for a simple, low-cost diagnostic test feasible to use in low-, middle- and high-income countries. To estimate the accuracy of the machine learning models, the researchers initially constructed the models with data from the discovery cohort, then confirmed the results by testing their performance on data from women in the validation cohort.

A prediction model using a set of nine urine metabolites was highly accurate, the researchers found. These urine markers, in samples collected before week 16 of pregnancy, strongly predicted who later developed preeclampsia. The performance of the test was measured by a statistical standard used in machine learning known as area under the characteristic curve. An AUC of 1 for a test with two possible outcomes indicates perfect prediction, whereas an AUC of 0.5 indicates no predictive value, the same as the results obtained from a coin toss. For the urine markers, the AUC was 0.88 in the discovery cohort and 0.83 in the validation cohort, indicating high prediction capability.

Measuring the same set of urine metabolites in samples collected throughout pregnancy produced similar predictive power, with an AUC of 0.89 in the discovery cohort and 0.87 in the validation cohort.

The researchers confirmed that their model had stronger predictive power than using only clinical features linked to a pregnant woman's preeclampsia risk, such as chronic hypertension, high body mass index and carrying twins.

A set of nine proteins measured in blood performed almost as strongly, with an AUC of 0.84.

The researchers also created a predictive model that combined participants' clinical features with urine metabolites, which enabled them to predict preeclampsia starting early in pregnancy with an AUC of 0.96. The clinical features in the combined model are data that are already collected as part of standard medical records, such as patients' age, height, body mass index and pre-pregnancy hypertension.

"This data collection is routine and could serve as the first level of triage," Agheeapour said. "We envision that patients whom the data show as at risk could receive the more extensive urine assay."

Uncovering the disease biology

Stanford Medicine researchers are also opening windows into the biology of preeclampsia. Another study, published in February in *Nature*, used cell-free RNA measurements to reveal biological clues as to how preeclampsia originates.

"The ability to eavesdrop on the conversation during pregnancy, synchronously measuring molecules from the pregnant woman, fetus and placenta, is very helpful for giving us hints about what biological changes contribute to the disease," said Mira Moufarrej, Ph.D., lead author of the Nature paper, who was a graduate student in bioengineering when the research was conducted. The paper's senior author is Stephen Quake, DPhil, professor of bioengineering and of applied physics.

"The most striking changes occurred before 20 weeks' gestation, whereas a preeclampsia diagnosis is usually made at 30-plus weeks of pregnancy," Moufarrej said. "That was surprising. We would expect

changes in gene signals when you see clinical symptoms, and this was happening much earlier in pregnancy."

Using 404 blood samples from 199 pregnant women, Moufarrej and her colleagues identified a set of 18 genes whose activity in early pregnancy predicted the development of preeclampsia.

The genes are consistent with what is known about the biology of how the disorder develops, she noted.

Scientists hypothesize that in preeclamptic pregnancies, the placenta doesn't fully develop; its blood vessels may be too small. At first, this is OK because the fetus is small and doesn't need much nutrition.

"But later in pregnancy, the fetus has grown, sending signals for more nutrition," Moufarrej said. "At that point, the only solution to small blood vessels is more blood flow, so we see high blood pressure." In severe cases, the pressure can lead to a premature separation of the placenta from the uterine lining, creating an emergency in which the baby must be delivered immediately.

The gene activity signals that Moufarrej and her colleagues identified came from genes involved in pathways consistent with the development of preeclampsia, such as tissues related to the endothelial system, placenta and brain. (The brain is relevant because full-blown eclampsia causes seizures.) The scientists plan to use the work as a foundation for future studies into the way the condition develops.

Worldwide benefits

The scientists involved in both studies will validate their predictive tests in much larger, more diverse populations of women, with the goal of creating tests for universal use.

Knowing more about how preeclampsia develops, and how to predict it, could have profound benefits for the world's most vulnerable moms, the researchers said, noting that an estimated 86% of maternal deaths worldwide occur in Asia and sub-Saharan Africa.

"This is where this type of test is really needed, where resources are very scarce," Marić said. Unlike women in high-income countries, many women in low-income regions give birth far from hospitals, limiting their access to emergency care when they show symptoms of preeclampsia or eclampsia. "If we can identify which pregnancies are at high risk early on, we can help get those women to health care facilities and prevent deaths."

More information: Ivana Marić et al, Early prediction and longitudinal modeling of preeclampsia from multiomics, *Patterns* (2022). DOI: 10.1016/j.patter.2022.100655

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