

Epigenetic Biomarkers May Help Assess Preterm Birth Risk

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BALTIMORE – DNA methylation profiles in buccal cells from couples may indicate their inherent risk of a pregnancy with preterm birth, according to researchers from Washington State University and their collaborators.

In an early exploratory study published last week in [Scientific Reports](#), Michael Skinner, director of the Center for Reproductive Biology at WSU, and colleagues identified changes in DNA methylation in both the mother's and father's buccal cells that were linked to preterm birth, promising potential biomarkers that could be harnessed toward prenatal testing.

According to Skinner, about 10 percent of pregnancies in the population will be preterm, "but there are no really efficient biomarkers out there to [predict preterm birth] early in pregnancy at all." Preterm birth could interfere with a newborn's normal development and result in a "significant increase in later-life disease," he said, including cognitive disabilities, seizures, visual and hearing impairment, and cardiovascular problems. Therefore, finding a reliable biomarker to help prognosticate preterm birth would be "a fairly significant advance," he added.

To achieve that, Skinner's team conducted an epigenome-wide association analysis to capture differential DNA methylation regions, or DMRs, in 21 control term birth and 19 preterm birth father-mother-infant triads recruited from the Indiana University hospital system. Specifically, the researchers conducted methylated DNA immunoprecipitation, or MeDIP, on the DNA samples followed by Illumina sequencing to profile DNA methylation.

Because DNA methylation signatures are heritable and exist in almost all cell types, they afford researchers "a better genome-wide assessment" compared with studying individual genes or proteins and the opportunity to be studied in easily obtained samples, he added, such as the cheek buccal cells used in this study. "These are cheek swabs," Skinner noted, "so they're not invasive."

Through the analysis, the researchers found 165 buccal cell DMRs in mothers of preterm babies that were distinct from mothers who carried their children to full term. "Surprisingly, many of the epigenetic shifts that were observed in the mother were also transmitted to the premature female babies," said Skinner, based on a comparison of maternal DMRs with 136 DMRs of female children. Interestingly, the study also found 73 paternal DMRs, suggesting potential paternal contributions to preterm birth, while the DMR association in male babies was "negligible."

"I think it's a really interesting approach to look at DNA methylation," said Lydia Shook, an obstetrician-gynecologist at Massachusetts General Hospital who specializes in maternal-fetal medicine. "DNA methylation is something that's inherited," she said; therefore, it can hint at "unmodifiable" risk factors associated with preterm birth.

According to Shook, despite the prevalence of preterm birth, clinicians currently "really don't have a great handle on how to predict who's at risk for preterm birth, and then also to prevent it." Especially with women who are pregnant for the first time, she pointed out, assessing the risk for preterm birth can be hard due to the lack of previous pregnancy history. Shook said there are some clinical indications, such as previous medical history, short cervix length under ultrasound, or dilated cervix in the middle of pregnancy without symptoms of labor, that may offer clinicians clues of impending preterm birth, but these measures are "imperfect" and can at best "identify the process that's already taken place."

As a result, Shook said for preterm birth, clinicians "really just monitor the mom's symptoms through pregnancy" under most scenarios. Even if she has symptoms of preterm labor, they are often "pretty far down the line," she added.

That said, Shook thinks the paper's DNA methylation approach "is a very interesting proof of concept," and the method of using cheek swabs "is definitely an easy way to collect the sample." However, she said, "the question is how challenging or expensive is it to run the analysis? I think that's where the trouble is." Additionally, because this study is for now "much more exploratory" and "hypothesis-generating," she said, further validations of the results in "much larger cohorts" are needed, which would be "critical to knowing how generalizable the information is."

Skinner said the team's goal moving forward is to conduct "larger clinical trials" with hundreds of patients to "confirm or enhance this signature." Although this early-stage study did not include a cost analysis, Skinner said he imagines the price tag for a future test based on the method described in this study "would be more like in the hundreds, not thousands." This test "would be much more affordable to the general public," he said. "Otherwise, it wouldn't have as much use."

Thomas McElrath, a maternal-fetal medicine specialist at Brigham & Women's Hospital, said one of the advantages of this study is that it "chose to look at the larger chunk of the problem" of preterm birth, which is spontaneous preterm deliveries without clear medical reasons.

Although there are "lots of investigations" for finding predictive biomarkers for preterm birth, he said, there is not much yet "in terms of what I have at my fingertips when I walk into the hospital tomorrow morning."

According to McElrath, who is also researching biomarkers to predict adverse pregnancy outcomes, the nature of DNA methylation means that the potential markers discovered in this study describe the "inherent propensity" of a mother's preterm delivery, unlike most RNA and protein-based biomarkers, which are believed to "somehow at least be involved in or triggered by the causal pathway" to preterm birth.

As a result, he pointed out, these biomarkers can potentially infer preterm birth probabilities but not diagnose it. "It's like if you have very high cholesterol," he explained. "You are at high risk of heart disease, but that doesn't mean you're going to get heart disease."

Moreover, McElrath cautioned that, in general, it is "incredibly important" for researchers to be aware of the subtypes within preterm birth when trying to derive biomarkers, especially for studies with a smaller cohort. Spontaneous preterm birth has many different associated components, such as infection and uterine physiology, he explained. "If we try to [look for] one biomarker to interpret what ultimately may be different initiating causes," he said, "then you're less likely to find a useful biomarker."

Skinner also emphasized that the epigenetic markers identified in this study can be used "just for the association with the disease" and "are not involved in the developmental etiology or origins of the disease."

Ultimately, he hopes to find an "industrial partner" that would commercialize the biomarkers and make them available to the public. For that, Skinner said the team is currently "in the process" of applying for a patent on the discoveries associated with this study.

Meanwhile, discoveries of other potential preterm birth biomarkers from both academic and commercial research labs are abounding. For instance, South San Francisco, California-based startup Mirvie reported in [Nature](#) in January that maternal cell-free RNA found in the blood plasma during pregnancy could help predict [risk of preeclampsia](#), which can lead to preterm birth, months before symptoms arise. McElrath was a senior author of that study. Additionally, researchers from Canada's Princess Margaret Cancer Centre and the University of Toronto also recently reported the prognostic utility of cell-free methylated DNA profiles in gauging pregnancy outcomes.

With the burgeoning biomarker investigations, McElrath noted that we're still in "such an early phase of development" that it is difficult to tell yet which marker is better. He also believes many different studies are necessary, as they not only bring "a fruitful conversation about risk stratification" but also help "generate increasing insights into the underlying biology," which he said makes the field fascinating.

"I tell my residents and my trainees that the way they're going to practice obstetrics when they are my age in their careers is going to be different than the way I'm practicing obstetrics," he added.

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