Metabolomic prediction of late-onset preeclampsia: Bahado-Singh et al

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The article below summarizes a roundtable discussion of a study published in this issue of the Journal in light of its methodology, relevance to practice, and implications for future research. Article discussed:

Bahado-Singh RO, Akolekar R, Mandal R, et al. First-trimester metabolomic detection of late-onset preeclampsia. Am J Obstet Gynecol 2013;208:58.e1-7.

DISCUSSION QUESTIONS

- How can metabolomics be used to identify biomarkers?
- What were the authors' aims?
- What was the study design?
- What were the statistical challenges?
- What information is presented in the tables and figures?
- What additional research is needed?

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Preeclampsia occurs in 5-8% of pregnancies, most commonly presenting at term as late-onset disease. Primary prevention is an enticing goal, but any strategy would require detection of high-risk women early in pregnancy. In a new study, Bahado-Singh and colleagues demonstrated that metabolomics might help distinguish these patients during the first-trimester.

Application of metabolomics

In short, metabolomics is the comprehensive study of metabolites; for example, the ways in which these small molecules change, interact, or react to modifications in the body's cells, tissues, or fluids. The field, born in the 1970s, flourished after the human genome was sequenced because investigators could then link metabolite measurements to the genome.

Bahado-Singh and collaborators used metabolomics to look for first-trimester biomarkers of late-onset preeclampsia and to examine their accuracy in predicting late-onset preeclampsia. In addition, they assessed whether metabolomics could be used to discriminate between early- and late-onset preeclampsia. Journal Club members appreciated the possible clinical implications of this investigation: women who are known to be at high-risk for preeclampsia before they are well into a pregnancy would be candidates for future preventative interventions. They also suggested that metabolites most associated with late-onset preeclampsia could play a role in its pathophysiology, and if so, they could serve as targets for research into therapeutic interventions.

Predictive modeling

Statistically significant differences in levels of 17 metabolites were noted between women with late-onset preeclampsia and controls. The most powerful group discriminators were glycerol, carnitine, and methylhistidine, all of which were increased in women with late-onset preeclampsia. Predictive models examined possible relationships between these and other metabolites, maternal demographics, and outcome.

Predictive modeling combines independent variables, often using logistic regression, to create a single model that can predict an outcome of interest. Then sensitivity and specificity of the models can be assessed. For models that incorporate continuous or ordinal data, receiver operating characteristics curves can be created by plotting the sensitivity against the false positive rate, computed as 1-specificity. The calculated area under the curve indicates the model's predictive ability; 1.0 represents a perfect test and 0.5, a test that does not predict the outcome of interest any better than chance. Models that incorporate different sets of variables to forecast the same result can be compared using each model's test characteristics.

For this study, 1 model was constructed with genetic computing, which is particularly useful in metabolomics because it sifts through many variables, determining the optimal number that should be used to achieve the best possible prediction. Another model used logistic regression and a larger number of subjects. The researchers noted that "significant diagnostic accuracy" was achieved whether metabolite levels were used alone or in combination with demographic information. However, while both models offered high specificity, the logistic regression models had much lower sensitivity. Clinically, both sensitivity and specificity of a test are important. If

an effective intervention were to be discovered for the prevention of late-onset preeclampsia, it would be important that a diagnostic be both sensitive—able to identify most of those at high risk—and specific; that is, capable of recognizing most of those who are not truly at high risk. Practitioners would not want to miss women likely to develop preeclampsia or unnecessarily treat those who have a positive test but are unlikely to become ill.

Need for validation

Journal Club participants agreed that while further investigation is needed to validate the results of this study in other populations, the work was well-designed and provocative. As the authors point out, other investigators have identified different metabolites linked with preeclampsia. In part, this is because of variations in technique, metabolites examined, and the outcome under investigation (ie, early vs late vs all preeclampsia). Yet, different metabolites may be identified when the same analysis is performed in other populations. Because late-onset preeclampsia is a clinically heterogeneous disease with varied phenotypes, a test that correlates first trimester metabolites with each type would also be of interest. Overall, the application of metabolomics to the study of obstetric complications like preeclampsia is a fascinating area of research. ■