However, there were no nonpregnant women as controls in this study. What are the background metabolite signatures in women? Are there any differences in the metabolites between the 2 groups (including the 3 BMI strata) in the nonpregnant state? How are they changed when pregnancy occurs? Are there different pattern changes for the 2 groups? Because there is no clear associations with gestational age at sampling for the metabolites evaluated, their levels in early pregnancy may reflect prepregnancy status rather pregnancy-related status.[4] This waits to be verified by measuring the metabolite levels in these subjects before or after pregnancy. Accordingly, disclosing the trajectories of the metabolites in the blood around conception may be more valuable for both early prediction and understanding the pathophysiology of the disease.

Efforts have been directed to understand the pathology underlying preeclampsia, which will lead to more superior strategies for early prediction. All predictive biomarkers need to be validated in larger studies with a heterogeneous population to ascertain the potential for their use in early pregnancy. The prediction of preeclampsia before symptom onset could guide the prophylactic use of potential therapeutic agents such as low-dose aspirin (Figure). ■

Yu Yang, BSc
Dong-Zhi Li, MD, PhD
Guangzhou Women and Children's Medical Center
Guangzhou Medical University
Guangdong Provincial Clinical Research Center for Child Health
Jinsui Rd 9
Zhujiang New Town
Guangzhou 510623
China
lidongzhi2013@aliyun.com

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A step closer to using metabolite biomarkers to improve early pregnancy prediction of preeclampsia

We appreciate the effort taken by Yang and Li to constructively engage with our article recently published in the *American Journal of Obstetrics & Gynecology*.[1]

The main critique leveled by Yang and Li on our work was regarding the absence of longitudinal metabolite biomarker data, more particularly, the absence of comparator prepregnancy data.

We agree with Yang and Li that such data would be particularly instructive in elucidating whether our findings mainly reflect the existence of different (subclinical) prepregnancy preeclampsia risk profiles instead of reflicting a differential biomarker response indicating preeclampsia risk during early pregnancy across women as a function of their body mass index (BMI).

As highlighted by Yang and Li, we reported the apparent lack of an association between metabolite levels and gestational age at sampling for all but 1 metabolite. In our study, we also confirmed the use of metabolites and metabolite ratios known to be associated with cardiovascular risk outside pregnancy[2] as (preterm) preeclampsia biomarkers, especially when the maternal BMI class was considered in the evaluation. Based on these observations, one can indeed speculate that our findings in early pregnancy may chiefly reflect existing, yet thus far unaccounted for prepregnancy risk profiles.[3] If confirmed, and by inference, our data may equally suggest that one should also account for patient BMI before conception to unmask different preeclampsia risk profiles in the prepregnancy period.

Although answering the longitudinal research question fielded by Yang and Li will certainly add to the understanding of exactly what (patho)physiological information is contained in early pregnancy maternal metabolite levels, the intention of our effort was to identify biomarkers that may improve preeclampsia risk prediction. With clinical use in mind, it is important to use blood samples that were collected under the current clinical care conditions. We think that the size of the study population and the broad racial and ethnic representation within the population add credence to our biomarker findings.

Like Yang and Li depict in their Figure, we also considered metabolite biomarkers as possible candidates to complement the established risk parameters to further improve early-pregnancy preeclampsia prediction, which in turn will help clinicians to stratify pregnant women more accurately to receive risk-modifying interventions like prophylactic aspirin treatment, which was effectively demonstrated by our group members (A.S. and K.N.) and colleagues in the Aspirin for Evidence-Based Preeclampsia Prevention trial.[4]

Unlike Yang and Li, we believe that the insight that metabolite biomarkers can be maternal phenotype specific will hasten the integration of the use of metabolites in existing preeclampsia risk algorithms and incrementally improve preeclampsia prediction. ■

Robin Tuytten, PhD
Metabolomic Diagnostics
Cork, Ireland

Argyro Syngelaki, PhD
Harris Birthright Research Centre for Fetal Medicine
King's College Hospital
London, United Kingdom

Grégoire Thomas, PhD
SQU4RE
Lokeren, Belgium

Kypros H. Nicolaides, MD
Harris Birthright Research Centre for Fetal Medicine
King's College Hospital
16-20 Windsor Walk
Denmark Hill, London SE5 8BB
United Kingdom
kypros@fetalmedicine.com

R.T. is an employee of Metabolomic Diagnostics. G.T. is the owner of SQU4RE, an independent Statistics and Data mining provider. G.T. and R.T. are named inventors on several Patent Applications regarding the use of metabolites to predict preeclampsia risk. The associated rights are assigned to Metabolomic Diagnostics. A.S. and K.N. report no conflict of interest.

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