Maternal Microbial Metabolites and Risk of Fetal Growth Extremes: A Longitudinal Multi-Racial/Ethnic Cohort Study

Rana Chehab,[1] Adrienne Kwok,[2] Oliver Fiehn,[3] Ines Thiele,[4] Amanda Ngo,[1] Dinesh Barupal,[5] Charles Quesenberry,[1] Assiamira Ferrara,[1] and Yeyi Zhu[1]

[1]Kaiser Permanente Northern California; [2]University of California, Berkeley; [3]University of California, Davis; [4]National University of Ireland, Galway; and [5]Icahn School of Medicine at Mount Sinai

Objectives: Fetal growth extremes [small- and large-for-gestational age (SGA and LGA)] represent high-risk phenotypes for cardiometabolic disorders. Metabolomic profiling of the in-utero milieu may elucidate pathophysiology of fetal growth extremes and inform dietary recommendations and upstream risk factors. We aimed to identify microbiome-derived metabolites associated with SGA and LGA.

Methods: A random sample of 140 SGA, 134 LGA and 140 appropriate for gestational age (AGA) was drawn from the Pregnancy Environment and Lifestyle Study cohort. Using fasting serum at gestational weeks (GW) 10–13 and 16–19, 1167 known metabolites were measured by gas and liquid chromatography (LC)/time-of-flight mass spectrometry (TOF-MS) and hydrophilic interaction LC/quadrupole TOF-MS, of which 165 microbial metabolites were linked with the Virtual Metabolic Human Database. After adjusting for sociodemographic, lifestyle, reproductive history, and clinical factors, we identified significant pathways associated with risk of SGA and LGA vs. AGA using chemical similarity enrichment analysis, controlling for the false discovery rate (P_{FDR}).

Results: At GW 10–13, branched-chain amino acids (AA), dicarboxylic acids (DA) and medium-chain hydroxy acids were positively, while phosphatidylcholines, saturated fatty acids (FA) and glucogenic AA were inversely associated with SGA risk (all $P_{FDR} < 0.01$). At GW 16–19, positive associations of branched-chain AA and DA and inverse associations of saturated FA with SGA risk persisted, while unsaturated triglycerides (TG) were inversely associated with SGA risk (all $P_{FDR} < 0.01$). At GW 10–13, glucogenic AA, DA, hippurates, phenylacetylglutamine and cresols were positively, whereas phosphatidylcholine and unsaturated TG were inversely associated with LGA risk (all $P_{FDR} < 0.04$). At GW 16–19, carnitine, saturated TG, cyclic AA, DA, glyceric acids, phenylacetylglutamine and cresols were positively, while aromatic, basic and sulfur AA, sugar alcohols, phosphatidylcholines and unsaturated TG were inversely associated with LGA risk (all $P_{FDR} < 0.05$).

Conclusions: Distinct microbial metabolites in early to mid-pregnancy are associated with SGA and LGA risk, calling for further investigation into microbiome-metabolome-host interactions.