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Metabolic profiling and targeted lipidomics in small for gestational age and fetal growth restriction

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Objective

While fetal smallness is, overall, associated with poor perinatal outcomes, small fetuses can be clinically categorized under two phenotypes: small for gestational age (SGA) and fetal growth restriction (FGR). SGA is usually associated with near-normal perinatal outcomes, whereas FGR is characterized by fetoplacental Doppler changes and a higher risk of fetal death and poor perinatal outcome. It is unclear whether these clinical phenotypes are different entities or represent variable degrees of severity of the same condition. Large-scale studies of metabolites (metabolomics) are key to understanding cellular metabolism and pathophysiology and might aid in the identification of specific changes in metabolites classes and subclasses that underpin metabolic responses to pathologic conditions. The objective of this study was to characterize metabolic profile changes in maternal and umbilical cord blood plasma in full-term singleton gestations with different clinical phenotypes of fetal smallness.

Methods

Prospective cohort study in singleton term gestations including 28 normally grown fetuses and 52 small fetuses (diagnosed >32 weeks and delivered >37 weeks) sub-classified into small for gestational age (SGA) (if birthweight was between the 3rd and 9th centile and had a normal fetoplacental Doppler; n=25) and FGR (if birthlweight was <3rd centile and/or abnormal cerebroplacental ratio or uterine artery Doppler; n=27). Maternal and cord blood plasma samples were used for NMR-based metabolic fingerprinting and profiling. First, a non-targeted approach was used to identify discriminatory spectral regions, based on supervised, multivariate analyses. Then, forefront methods of quantification for low-molecular weight (LMW) metabolites, lipoproteins, choline compounds and glycoproteins were applied.

Results

The most relevant differences between the study groups were detected in lipids. Lipoprotein profiles showed significantly lower plasma concentrations of cholesterol-intermediate density lipoprotein (IDL) (-17%), triglycerides-IDL (-13%) and –high-density lipoprotein (HDL) (-18%) in mothers of small fetuses (both, SGA and FGR) compared to controls ($p<0.05$; all). SGA and FGR fetuses had significantly higher plasma concentrations of cholesterol and triglycerides. Specifically, FGR fetuses showed increased low, very low-density lipoprotein [LDL (+32%), VLDL (+56%), and IDL (+24%) compared to controls ($p<0.005$; all), as well as increased VLDL particle types (large, medium and small), in a severity-graded manner ($p<0.05$). Similarly, changes in phosphatidylcholines and glycoproteins were prominent in SGA and FGR cases indicating significant alterations in their abundance and biophysical properties. Analysis of LMW metabolites additionally revealed significant changes in late-FGR subjects, including formate, histidine, isoleucine and citrate, with preserved glucose concentrations.

Conclusion

Comprehensive metabolic profiling confirmed previous studies reporting that mothers of small fetuses present substantial reductions in lipid metabolites compared to controls, suggesting a failure in the maternal metabolic adaptation to pregnancy. In contrast, small fetuses have substantial increases in lipid metabolites, which suggests a tentative compensatory mechanism to undernutrition. SGA and FGR presented a similar pattern of changes in all evaluated maternal and fetal parameters, supporting the notion that they represent different degrees of severity of the same underlying condition.