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Microbiota be nimble

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We appreciate the data-rich metatranscriptome paper on the enzyme production capacity of maternal and infant gut microbiota published recently in EBioMedicine by Gosalbes et al. from a sample of Spanish maternal-infant dyads [1]. As noted, the added value of their paper is its contribution to new understanding of the critical changes to gut microbial function that occur before and after pregnancy and during the first year of life, for which there is a paucity of information.

The main finding of the Gosalbes et al. study was that enhanced enzymatic activity found in fecal samples during the last trimester of pregnancy related to carbohydrate utilization by gut microbiota. This was proposed to be a function of the hyperglycemic state and leaky gut of later pregnancy, which made the gut lumen hyperglycemic as well. Equally plausible, could be greater maternal intake of starch and sugars in the last trimester, which would directly enhance substrate availability to microbiota in the gut. As dietary carbohydrate increases in later pregnancy, micronutrient intake declines [2], which begs the question as to whether other factors (e.g., deficiencies or excesses of cofactors such as iron) are key influencers of microbiome metabolism beyond carbohydrate substrate availability.

Understandably, Gosalbes et al. focused their discussion on differences in the gut microbial transcriptome of pregnancy compared to that of the postpartum period since the former constituted the majority of study findings. However, it is worth noting that maternal gut microbiota play an essential role during breastfeeding to produce metabolites, such as amino and short-chain fatty acids, which make their way into breast milk and support the nursing infant [3]. The Gosalbes et al. study included mothers who were breastfeeding. Relative to pregnancy, the gut microbial transcriptome in the postnatal period of study mothers was enriched in functions related to the synthesis of histidine, aromatic amino acids, fatty acids and phospholipids. On the other hand, Jost el al reported that maternal fecal levels of short-chain fatty acids in the postnatal period were maintained at the same levels as those in the last trimester of pregnancy, despite concomitant reductions in fecal streptococci and enterobacteria [4], microbiota which increase in abundance towards the end of pregnancy [5]. This constancy in metabolite production during a period of change in microbial composition and in enzyme activity highlights the plasticity of microbiota in the synthesis of metabolites in response to the physiology of birth and breastfeeding.

In our opinion, the most interesting finding was the upregulation of enzymes in the phosphortrans-butyrylase pathway of butyrate production during the first few months of infant life. As the authors aptly noted, this pathway is prominent in the butyrate-producing microbiota of the Firmicutes phylum, which are normally low in abundance soon after birth [6,7]. Here it is worth pointing out that other microbiota which do not normally produce butyrate have the capacity to switch to this pathway under more aerobic (soon after birth) or acidic (during breastfeeding) conditions [8]. Again, the Gosalbes et al. findings demonstrate the nimbleness of human microbiota under the ever-changing conditions of the infant gut.

As we end our commentary, we wish to turn the reader's attention to some of the technical aspects of this transcriptomics study. Observed changes in enzyme activity of microbiota conceivably reflect gut microbial strategies for survival upon exposure to oxygen or other substances in the air, or to a colder temperature after sampling from the warm, anaerobic environment of the gut [9]. For this reason, some may argue that fecal transcriptomics is not a valid method to monitor changes in the human gut microbiome. But the larger issue, which in epidemiologic terms is known as measurement error or misclassification bias, is whether study findings could be biased by the process for fecal sample collection which generated the RNA transcript data. Differential misclassification bias occurs when the error rate in the collection process differs according to the source and place of the sample collection (e.g., mother - hospital versus infant - home). Simply put, misclassification bias would result if the retrieval and storage of fecal samples led to systematic differences in reported enzyme pathways. This would lead readers to question, for example, whether higher enzyme activity in carbohydrate metabolism of the maternal gut microbiome in the prenatal versus the postnatal period could possibly be due to greater air contamination or drop in temperature of the prenatal samples. The addition of the RNA stabilization agent after fecal samples were frozen (versus the usual practice of adding the stabilizer beforehand) is also an issue of bias but since it affects all samples, the end result would be non-differential misclassification bias which ultimately minimizes group differences.

Author disclosure

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