EDITORIAL

Maternal Microbiota, Prepregnancy Weight, and Mode of Delivery

Intergenerational Transmission of Risk for Childhood Overweight and Obesity

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Pediatric overweight (OW) and obesity (OB) are a major public health problem, reaching pandemic proportions. Among the multiple factors involved in the development of childhood obesity, data accrued during the last few years indicate that pediatric OWOB may be a result of intergenerational transmission.[1]

Related article

Maternal weight, mode of birth delivery, and composition of the neonatal intestinal microbiota (IM), which tends to be affected by maternal factors before pregnancy, appear to play an increasingly important role.[2] However, published data are sparse and sometimes inconsistent.

Maternal Weight

A 2017 Norwegian study of 552 children found that differences in the composition of the maternal IM at the time of delivery associated with prepregnancy OWOB and gestational weight gain were either absent or at undetectable levels in most of the infants aged 4 to 10 days.[3] However, a 2010 Finnish study of 42 women with overweight (body mass index [BMI, calculated as weight in kilograms divided by height in meters squared], ≥25) and normal weight (BMI <25) found that the composition of their infants' IM (checked at age 1 and 6 months) was associated with BMI and gestational weight gain.[4]

Mode of Birth Delivery

A 2015 study of 98 full-term Swedish infants found that 72% of the IM species of vaginally delivered infants matched the species in maternal stool vs 41% of the IM species of infants born by cesarean delivery (mother checked at delivery and infants during the first days of life and at 4 and 12 months of age).[5] Consistent with the findings of the Swedish study, Mueller et al[6] reported that excess maternal prepregnancy BMI was associated with acquisition of neonatal microbiota (n = 74 infant samples of first neonatal stool after meconium) among infants delivered vaginally but not in those born by elective cesarean delivery without membrane rupture.

Overall, the results of studies on the composition of infant and mother IM are inconclusive; the different times when infant fecal samples were obtained appear to be an important limiting factor. With this background, we found that the results reported by Tun et al[7] in this issue of *JAMA Pediatrics* to be of particular interest. Their observational study of 935 full-term infants in the Canadian Healthy Infant Longitudinal Development birth cohort adds important information to the growing field of intergenerational transmission of obesity risk. In particular, the authors provide data suggesting that mode of birth delivery and infant IM are cooperatively involved in the transmission of maternal OWOB to offspring.[7] Compared with infants delivered vaginally to mothers with normal weight without intrapartum antibiotic prophylaxis, infants of mothers with OWOB who had a cesarean delivery had a 5-fold risk of overweight at 1 year of age. Interestingly, vaginally delivered infants of mothers with OWOB had a 3-fold risk of having overweight at age 1 and 3 years. These results were adjusted for infant sex, socioeconomic status, maternal race/ethnicity, maternal prenatal asthma, maternal prenatal smoking, breastfeeding status, use of oral antibiotics (at age 0-12 months), and pet exposure. Akin findings were recently reported from another large observational study of 1441 racially and ethnically diverse mother-child dyads in the Boston Birth Cohort, in which cesarean delivery and prepregnancy OWOB were associated with childhood OWOB.[8]

However, the work by Tun et al[7] appears particularly interesting because they used sequential mediation analysis (a feature used in other fields but that had not been previously applied to microbiome studies) for their large prospective cohort, which allowed them to successfully examine 2 original, relevant issues. First, they identified indirect or mediating effects of infant fecal abundance of *Lachnospiraceae* bacteria (phylum Firmicutes) in children with OWOB with a mean age of 3.7 months, born to mothers with OWOB after either vaginal or cesarean delivery. Second, the authors established that maternal BMI and cesarean delivery together affect the composition of the initial microbial communities in offspring with OWOB.

The abundance of Firmicutes in the children with obesity in the study by Tun et al[7] had already been mentioned in previous studies that had addressed other issues. Thus, this finding leads to the interesting question of how are *Lachnospiraceae* involved in the transgenerational transmission of maternal OWOB?

We believe that these following points should be emphasized:

- *Lachnospiraceae* and *Ruminococcaceae* are major taxonomic groups in the human gut microbiota that degrade complex polysaccharides to short-chain fatty acids, including ac-

etate, butyrate, and propionate, which can be used for energy by the host.[9]

- *Ruminococcus* species, especially *R gnavus*, have been reported to be important actors in early infant gut colonization, which varies across individuals and is not strictly linked to the type of feeding or mode of delivery.[10] This finding is particularly relevant because *Ruminococcus* species and *Bifidobacteriaceae* share metabolic pathways that are involved in the degradation of complex sugars and mucin, therefore supporting the belief that the release of sugars resulting from mucin degradation might be important for the succession of other bacteria.
- *R gnavus* in particular produces iso-bile acids, which have a detoxification pathway that positively affects the growth of one of the predominant genera in the human gut, *Bacteroides*.[11]
- Species belonging to the *Bacteroides*, *Lachnospiraceae*, and *Bifidobacterium* coabundance groups and the alpha diversity of gut microbiota continue to change sequentially with age in individuals younger than 20 years, reflecting the maturation process of the human gut microbiota.[12]

Maternal weight and metabolic hormone factors were further examined in association with the gut microbiome of women during pregnancy.[13] The blood and stool samples collected from 29 pregnant women with OW and 41 with OB at 16 weeks' gestation[14] moreover showed that the IM of women with OB (vs OW) tended to show slightly lower microbial richness (number of unique operational taxonomic units) and evenness (relative prevalence of various operational taxonomic units), which are 2 measures of alpha diversity. No difference was found for beta diversity or phylogenetic distance between the IMs of women with OW vs OB. However, comparison of the compositions of IM at the phylum level showed that women with OB (vs OW) had significantly higher relative abundances of Firmicutes and Actinobacteria and lower relative abundance of Tenericutes. At the family level, abundances of *Lachnospiraceae* and *Rikenellaceae* were positively correlated with maternal BMI. Although these results indicate that BMI and metabolic markers in pregnancy are associated with the composition of IM, the cross-sectional nature of the study could not clarify the direction of the association.

Interestingly, quite similar results were recently seen in another study[15] that explored the effect of maternal diabetes in pregnancy on the microbiome of the meconium of newborns of mothers with pregestational and gestational diabetes. The beta diversity of the microbiome of meconium of newborns of mothers with diabetes was significantly different from the beta diversity of the meconium of newborns of mothers without diabetes. The infants of mothers with diabetes moreover had meconium with a significantly higher abundance of Bacteroidetes (phylum), *Lachnospiraceae* (family), and *Parabacteroides* (genus) organisms and lower abundance of Proteobacteria (phylum) organisms.

The well-designed study by Tun et al[7] therefore has merits because of the addition of important information that supports the view that maternal BMI and cesarean delivery cooperate in shaping the microbial communities of early life, which are associated with the development of OWOB in their offspring. Nonetheless, their study has a number of limitations that should be taken into consideration by future confirmatory studies. In particular, a major limitation was the lack of maternal samples for IM analysis. Maternal vaginal and skin microbiota are also involved in the development of infant IM but were not studied. Infant stool samples were collected only once at a mean age of 3.7 months. Other stool samples collected at older ages (eg, age 12 months) might have allowed confirmation of the results, especially given the information that infant IM changes during the first year of life and that different factors affecting infant IM (eg, breastfeeding and early exposure to antibiotics) appear pivotal. Limited generalizability of the results (exclusive Canadian ethnicity) was also a limitation.

Despite the limitations of the study by Tun et al,[7] its strengths include the large study population. They found that richness in Firmicutes species and increased abundance of *Lachnospiraceae* were important for the intergenerational transmission of OWOB. Future studies are needed to confirm these results and to understand more deeply the multiple factors implicated in a hitherto still complex interplay. Further clarification of the mechanisms leading to the development of childhood obesity may pave the way to novel strategies for obesity prevention that include the interruption of intergenerational transmission of OWOB from mother to offspring.

ARTICLE INFORMATION

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REFERENCES

1. Ma RCW, Popkin BM. Intergenerational diabetes and obesity: a cycle to break? *PLoS Med*. 2017;14(10):e1002415.

2. Paolella G, Mandato C, Pierri L, Poeta M, Di Stasi M, Vajro P. Gut-liver axis and probiotics: their role in non-alcoholic fatty liver disease. *World J Gastroenterol*. 2014;20(42):15518-15531.

3. Stanislawski MA, Dabelea D, Wagner BD, Sontag MK, Lozupone CA, Eggesbø M. Pre-pregnancy weight, gestational weight gain, and the gut microbiota of mothers and their infants. *Microbiome*. 2017;5(1):113.

4. Collado MC, Isolauri E, Laitinen K, Salminen S. Effect of mother's weight on infant's microbiota acquisition, composition, and activity during early infancy: a prospective follow-up study initiated in early pregnancy. *Am J Clin Nutr*. 2010;92(5):1023-1030.

5. Bäckhed F, Roswall J, Peng Y, et al. Dynamics and stabilization of the human gut microbiome during the first year of life [published correction appears in *Cell Host Microbe*. 2015;17(6):852]. *Cell Host Microbe*. 2015;17(5):690-703.

6. Mueller NT, Shin H, Pizoni A, et al. Birth mode-dependent association between pre-pregnancy maternal weight status and the neonatal intestinal microbiome. *Sci Rep*. 2016;6:23133.

7. Tun HM, Bridgman SL, Chari R, et al; Canadian Healthy Infant Longitudinal Development (CHILD) Study Investigators. Roles of birth mode and infant gut microbiota in intergenerational transmission of overweight and obesity from mother to offspring

[published online February 19, 2018]. *JAMA Pediatr*. doi:10.1001/jamapediatrics.2017.5535

8. Mueller NT, Mao G, Bennet WL, et al. Does vaginal delivery mitigate or strengthen the intergenerational association of overweight and obesity? findings from the Boston Birth Cohort. *Int J Obes (Lond)*. 2017;41(4):497-501.

9. Biddle A, Stewart L, Blanchard J, Leschine S. Untangling the genetic basis of fibrolytic specialization by lachnospiraceae and ruminococcaceae in diverse gut communities. *Diversity (Basel)*. 2013;5(3):627-640. doi:10.3390/d5030627

10. Sagheddu V, Patrone V, Miragoli F, Puglisi E, Morelli L. Infant early gut colonization by lachnospiraceae: high frequency of ruminococcus gnavus. *Front Pediatr*. 2016;4:57.

11. Devlin AS, Fischbach MA. A biosynthetic pathway for a prominent class of microbiota-derived bile acids. *Nat Chem Biol*. 2015;11(9):685-690.

12. Odamaki T, Kato K, Sugahara H, et al. Age-related changes in gut microbiota composition from newborn to centenarian: a cross-sectional study. *BMC Microbiol*. 2016;16:90.

13. Singh S, Karagas MR, Mueller NT. Charting the maternal and infant microbiome: what is the role of diabetes and obesity in pregnancy? *Curr Diab Rep*. 2017;17(2):11.

14. Gomez-Arango LF, Barrett HL, McIntyre HD, Callaway LK, Morrison M, Dekker Nitert M; SPRING Trial Group. Connections between the gut microbiome and metabolic hormones in early pregnancy in overweight and obese women. *Diabetes*. 2016;65(8):2214-2223.

15. Hu J, Nomura Y, Bashir A, et al. Diversified microbiota of meconium is affected by maternal diabetes status. *PLoS One*. 2013;8(11):e78257.