Commentary

Mode of Delivery to the Brave New (Microbial) World: A Defining Moment for the Respiratory Microbiome?

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A R T I C L E   I N F O

The index event of birth has always been viewed as the most challenging physiologic adaptation of our lives. With the emergence of microbiome science, we have appreciated yet another critical transition that occurs at birth: the fetus exits the sterile (or at least low in microbial biomass (Funkhouser and Bordenstein, 2013)) environment of the womb to enter the outer world ecosystem with abundant microorganisms. This route of entry to the microbial world, or mode of delivery, can determine which of the mother’s microbes have the first shot at founding colonies within the baby’s body. Vaginal birth offers a prolonged exposure to vaginal and intestinal microbiota, whereas Caesarian section (C-section) directly exposes the fetus to skin and environmental microbes (Dominguez-Bello et al. 2010).

As the seeds of the developing infantile microbiome are planted at birth, the well-established downstream associations of C-section with childhood respiratory illness, such as asthma and respiratory infections (Black et al. 2015), may in fact reflect the effects of C-section on microbiota. With extensive evidence linking specific profiles of the respiratory microbiome of children with subsequent development of respiratory illnesses (Lynch and Boushey, 2016), Bosch et al. (2016) in this issue of EBioMedicine examine a logically emerging hypothesis: does C-section impact the evolution of the upper respiratory microbiome?

In this well-designed birth cohort study, the investigators prospectively followed 102 neonates born either vaginally or by C-section and repeatedly sampled their nasopharyngeal microbiome at regular intervals up to six months of age. Immediately after birth, the nasopharynx of babies was coated by a low biomass bacterial community of mixed origin, with species of presumed fecal and vaginal origin being more common in vaginally-delivered neonates. Following an outgrowth of Streptococcus viridans by 24 h after birth, neonates developed individual succession patterns of community composition and transitioned through four major bacterial clusters. Importantly, mode of delivery was not exclusively associated with any specific clusters, but instead with the rate by which children transitioned through different clusters to reach more stable community profiles. Thus, children born by C-section stayed longer in a Staphylococcus aureus-dominated cluster whereas vaginally-delivered children switched earlier to (more mature) profiles with Moraxella, Corynebacterium and Dolosigranulum, bacteria previously shown to be protective from respiratory illnesses (Biesbroek et al. 2014a; Teo et al. 2015).

Bosch et al. performed frequent sampling of the nasopharyngeal microbiome during the first 6 months of life, a period not well-covered by previous studies (Biesbroek et al. 2014a, 2014b; Dominguez-Bello et al. 2010; Teo et al. 2015). Thus, this study captured for the first time the most dynamic changes that occur within the first two months of life, and also showed that the observed patterns of microbiome evolution were independent of breastfeeding, a potential confounder during this early period. They further demonstrated that a transient abundance of Haemophilus species was associated with respiratory symptoms suggestive of infection, in accordance to previous studies (Biesbroek et al. 2014a; Teo et al. 2015).

These studies raise the key question of whether it is possible to detect microbiota signatures over time attributable to mode of delivery. If we think about the causal model at play, delivery is effectively placed at the very onset of progressive acquisition of microbiota by the “sterile” neonatal body, so that the effect of “seeding” microbiota by vaginal delivery or C-section can be directly measurable immediately after birth without confounding. Founding microbial communities would be expected to evolve over time, with differences related to mode of delivery. As time continues, microbiome evolution can be influenced by environmental exposures (such as breastfeeding, maternal health, diet). These exposures can be associated with the mode of delivery and consequently open the door to confounding, making it harder to detect true causal effects of delivery mode over time. Thus, it is critical to define these early, immediate effects of delivery type, although quite challenging to do so. The study by Bosch et al. was not able to reliably illustrate that immediate link. Only 15% of early samples had enough detectable DNA for sequencing, and the lack of maternal samples limits the ability to infer origin of bacteria. The inclusion of infant gut microbiota analyses in relation to the founding maternal bacterial profiles and the simultaneously evolving nasopharyngeal microbiome could be insightful in future studies. Nonetheless, the
authors were able to perform the most frequent neonatal sampling to date and applied advanced analytic methods to demonstrate a consistent, time-independent association between C-section and microbial evolution.

The results of this study and others on founding of the neonatal microbiome also raise the question of whether a vaginal microbial transfer approach could mitigate the aberrancy in the respiratory microbiome observed with C-section, as previously shown in a pilot study for the oral and skin microbiomes (Domínguez-Bello et al. 2016). However, it is premature to consider such approaches. Any causal effect of C-section on the respiratory microbiome, even if true, appears to be small, and the “vaginal seeding” approach, despite a rising “off-label” popularity, is still unproven for its safety and efficacy as an intervention (Cunnington et al. 2016). Careful study in the context of a clinical intervention trial is needed before claiming any ability to restore a “healthy” neonatal microbiome.

The methodologically sound study by Bosch et al. (Bosch et al. 2016) represents an important step forward in the field, highlighting the complexity and dynamic nature of the upper respiratory microbiome early in life, and demonstrating the expected patterns of evolution with vaginal delivery and C-section. With further careful study of the early effects of delivery mode on seeding microbial communities, we would be able to come closer to identify targets and interventions for assisting the “microbial maturation” of the vulnerable neonates in those cases of unavoidable C-sections.

Conflicts of Interest

No conflict of interest.

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