CESAREAN-SECTION AND THE DYSBIOSIS OF NEONATAL GUT MICROBIOME: ILL-EFFECTS, SIDE-EFFECTS, OR JUST EFFECTS?

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ABSTRACT: Our gut microbiota plays a fundamental role in our health and disease. The establishment of human gut microbiota during infancy is influenced by many factors among which delivery mode has the most prominent effect. Babies born by C-section harbor a different microbiota profile as compared to babies born vaginally. Coincidently, babies born via C-section are also found to be more predisposed to develop diseases such as asthma, obesity, type-2 diabetes etc. later in life, possibly because of abnormal microbiome spectrum. However, it still remains unresolved whether inclination to these maladies results from a lack of exposure to the mother’s (vaginal and perianal) microbiota during birth or from higher exposure to unsolicited microbes such as those acquired from environment, mother’s skin etc. Hence, further studies are still required to intensely examine the colonization pattern of infant gut microbiota with regard to birth mode and its comprehensive influence on infant’s long-term health, particularly scrutinizing the influence of confounding factors such as demographic, ethnic, genetic, parental, environmental, nutritional, gestational etc. Present mini-review aims to bring together some of the important evidences on the influence of birth mode on the acquisition and development of infant gut microbiota composition.

KEY WORDS: Birth Mode, C-Section, Gut Microbiome, Infant Microbiota, Vaginal Delivery

Thanks to the remarkable flurry of elegant and revolutionary researches over the past two decades, it has now become a very well established fact that our gut microbiome plays a fundamental role in numerous aspects of our health and many diseases (Kau et al., 2011; Wallace et al., 2011; Clemente et al., 2012; Tremoli and Backhed 2012; Tamburini et al., 2016). It had long been believed that the microbial colonization of the human gut starts immediately at and after birth; however, recent discoveries have demonstrated that the human intestine is colonized by numerous bacteria much before birth i.e. during fetal stages (Aagaard et al., 2014; Collado et al., 2016; Nagpal et al., 2016). Nevertheless, the baby is colonized much heavily at parturition as the newborn is exposed to the birth canal and is seeded with a wide variety of bacteria from mother’s vaginal, skin and perianal flora, followed by exposure to environmental bacteria, spores, antigens etc. (Fanaro et al., 2003). It is also now well documented that this pioneer microbiota is influenced by various factors such as gestational age, mode of delivery and feeding, maternal microbiome, maternal or neonatal antibiotic exposure during gestation as well as during birth, maternal diet and health during gestation, the surrounding environment, weaning time and the type of first solid-food, siblings, pets, etc. (Nagpal and Yamashiro, 2015; Nagpal et al., 2016; 2017; Tamburini et al., 2016). Among all these factors, the mode of birth (vaginal- or cesarean-delivery) has the earliest and the most profound impact on the perinatal and neonatal microbiome (Penders et al., 2006; Backhed et al., 2015; Bokulich et al., 2016; Chu et al., 2017; Nagpal et al., 2017).

For example, the gut microbiota of babies born vaginally is dominated by lactobacilli, Prevotella and some other species that are acquired from mother’s vaginal flora; whereas babies
delivered via C-section have no or much less population of these bacteria and alternatively have a dominance of staphylococci, propionibacteria or Corynebacterium acquired largely from the maternal skin (Dominguez-Bello et al., 2010). We have also recently reported that the Japanese babies born via cesarean-section possess significantly less population levels of Bacteroides fragilis group, bifidobacteria and lactobacilli and higher prevalence of pathobionts such as toxigenic Classtidium perfringens as compared to vaginally-born counterparts, and that these differences start building up as early as the first day of life and persist up to six months of age or even longer (Tsuj et al., 2012; Nagpal et al., 2016; 2017). Although these differences gradually decrease and eventually vanish by 3 years of age, some cesarean-associated bacterial indications may last even until seven years of age (Salminen et al., 2004), indicating that the early-life colonization might confer a competitive advantage to the microbial communities associated with the birth mode. Many studies on other population cohorts from Sweden, Italy and UK have also reported that compared to naturally-delivered infants, cesarean-born infants carry more Klebsiella, enterobacteria and clostridia, including the potential pathogens Classtidium difficile (Hall et al., 1990; Adlerberth et al., 2006, 2007; Penders et al., 2006). Very recently, in a bid to mitigate the aberrancies in the neonatal gut microbiome associated with C-section, a pilot study even attempted to expose the infants delivered by C-section to maternal vaginal fluids at birth via vaginal microbial transfer (Dominguez-Bello et al., 2016). Although the authors were able to partially restore the vaginal microbes at birth in C-section, the long-term health consequences of such an approach remain completely unclear. In another study, babies born via C-section were found to harbor fewer bifidobacteria and showed to mount a stronger humoral immune response (Huurre et al., 2008), thereby hinting that, as compared to cesarean-born babies, vaginally-born babies may have lower humoral and higher cellular immunity in early years. Together, these studies clearly show that the gut microbiota of babies born naturally is predominated by beneficial (e.g., bifidobacteria, lactobacilli) bacterial species, whereas cesarean-born babies are more predisposed to carry species (C. difficile, C. perfringens, E. coli etc.) that are linked to several diseases.

Interestingly, along the same timeline, many studies have reported that as compared to vaginally-born babies, cesarean-born babies are more prone to develop diseases such as allergies, asthma, adiposity and obesity, celiac diseases, Type 2 diabetes etc. during later years of life (Eggesbo et al., 2003; Laubereau et al., 2004; Bager et al., 2008; Thavagnanam et al., 2008; Pistiner et al., 2008; Huh et al., 2012; Sevelsted et al., 2015; Dogra et al., 2015; Mueller et al., 2016). Hence, it is reasonable to speculate that the cesarean-mediated dysbiosis in the gut microbiota could lead to aberrancies in the mucosal immune tolerance and response and hence might underlie the increased predisposition as well as incidence of these health maladies (Maynard et al., 2012), especially considering the fact that exposures to these bacterial clades have an important impact on host immunity. Indeed, the prenatal and perinatal intestinal colonization is a critically important process during which the immune system also goes through important development and maturation phases. Hence, it can be hypothesized that normal (or higher) levels of Bacteroides fragilis, bifidobacteria and lactobacilli in vaginally-born babies might bring about a different immune cell arrays (e.g. T-cell subsets) and circulation, whereas relatively lower carriage of these commensals and an alternatively higher levels of C. difficile, C. perfringens, E. coli etc. in cesarean-born babies could instigate a different immunological pattern that might predispose the host towards certain illnesses.

Accordingly, driven by these hypotheses, many studies have reported correlations between cesarean-instigated gut dysbiosis and increased susceptibility to several diseases (Eggesbo et al., 2003; Laubereau et al., 2004; Bager et al., 2008; Thavagnanam et al., 2008; Pistiner et al., 2008; Huh et al., 2012; Sevelsted et al., 2015; Dogra et al., 2015; Mueller et al., 2016). However, whether these correlations are causal and also what mechanisms/elements are underling/driving these associations remain to be demonstrated. As a result, it remains highly debatable whether C-section per se increases the disease predisposition later in life, and also whether these disease correlations are caused by a lack of exposure to the mother’s vaginal/perianal microbiota during birth or due to an increased exposure to other unsolicited bacteria e.g. from the environment, maternal skin etc. No doubt, a thoroughly careful and systematic validation of these observations and elucidation of the substitute risk factors is of critical importance since any error or discrepancy can attribute a consequence incorrectly to an improper source and hence could potentially mislead the direction of research related to the development of effective interventions.

Also, research focus is needed to deeply understand the indication of the delivery, especially considering the fact that the rate of cesarean deliveries is unnecessarily increasing at an alarming pace worldwide (Zizza et al., 2015). In fact, the rapidly increasing global prevalence of diabetes, obesity, and autoimmune and cardio-metabolic diseases over the last two decades has been speculated to be attributed, at least in part, to the corresponding upsurge in the rate of C-section deliveries (Eggesbo et al., 2003; Decker et al., 2010; Huh et al., 2012). Also, the reason why these correlations still remain debatable is the ambiguity of possible confounding factors inherently associated with the C-section (Aagaard et al., 2016). For e.g., mother’s consuming a high-fat diet during gestation and also the over-weight and obese mothers are more prone to deliver via C-section. At the same time, maternal high-fat diet and the resultant obesity affects the baby’s microbiome. Therefore, the independent effect of maternal diet, gestational obesity and the cesarean surgery on baby’s microbiome remains unclear. In addition, compared to vaginally-born babies, cesarean-born babies generally spend a longer time at the hospital post-birth and this could have various confounding effects such as higher exposure to the hospital ‘flora’, an abrupt breast-
feeding schedule during first few days of life, different array and duration of surrounding environmental exposures etc. on the baby’s microbiota. Also, women delivering via C-section mostly receive a different and longer regimen of antibiotics before, during as well as immediately after the delivery, which can have significant influence on the neonatal microbiome. Also, the array and magnitude of the mode of infant gut bacteria acquisition i.e., which bacteria coming essentially from mother and which from the environment (vertical vs. horizontal transmission) remains to be deciphered completely. Notably, whether and how the gut microbiota differs between elective vs. medically indicated cesarean sections remain to be delineated completely at the moment. Also, comprehensive understanding of the clear-cut routes and sources of various bacteria in the prenatal and neonatal gut would detangle some of these confusions while identifying novel and efficacious targets for preventing gut dysbiosis and associated ailments. Given that majority of studies use DNA sequence targeted methods to analyze the early life microbiota colonization, it also remains indistinct whether the prenatal microbial encounters involve ‘live’ bacteria or it is just in the form of dead bacteria or bacterial fragments as one of the nature’s ways of vaccinating the newborn against possible infections.

Nevertheless, the ever-mounting evidence that the fetal life is not essentially devoid of environmental stimulants clearly hints that the modulation of gestational, prenatal and perinatal environment might prove to be effective for beneficial modification of the host immunity, thereby underscoring the need for further research to examine the prospects of modifying the host epigenetics during early life and also to explore whether such epigenetic changes could also be induced not only during early life but also during later stages of life. Future studies that integrate diverse dynamics and features of the maternal and infant gut microbiomes as well as other potential expounding vs. confounding variables are clearly anticipated to decipher the mechanisms driving these correlations and to explore novel and effective strategies to prevent neonatal gut dysbiosis and related illnesses.

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