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Dysbiosis in Children Born by Caesarean Section

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Abstract
The rate of Caesarean-section delivery in the United States has increased by 60% from 1996 through to 2013 and now accounts for >30% of births [CDC, 2017]. The purpose of this review is to present the current understanding of both the microbial risk factors that increase the likelihood of a Caesarean-section delivery and the microbial dysbiosis that is thought to result from the Caesarean section. We provide examples of research into the impact of early-life microbial dysbiosis on infant development and long-term health outcomes, as well as consider the efficacy and the long-term implications of microbiome-based therapies to mitigate this dysbiosis. The steep rise in the Caesarean-section delivery rate makes it imperative to understand the potential of microbiota modulation for the treatment of dysbiosis.

Introduction

The gut microbiota plays a critical role in infant immune and metabolic development, and the mode of delivery is a major determinant of early life exposure and colonization [Madan et al., 2016]. The human gastrointestinal tract is essentially uncolonized in utero, so exposure to microbes during delivery and in the environment immediately following birth is key to the establishment of the microbiota. In the case of vaginal delivery, the infant is in contact with maternal vaginal and enteric contents [Rutayisire et al., 2016]. Vaginally delivered infants are colonized with microbes including *Lactobacillus*, *Prevotella*, *Bacteroides*, *Escherichia/Shigella*, and *Bifidobacterium* [Dominguez-Bello et al., 2010], which have been identified in vaginal and fecal samples from adult mothers. Microbial dysbiosis during pregnancy is often associated with complications that can indicate Caesarean-section delivery, such as preterm birth, extremes of maternal body mass index (BMI), infection, extremes of infant size, and gestational diabetes [Neu and Rushing, 2011]. Birth via Caesarean section interrupts the normal pattern of microbial colonization; infants

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are no longer exposed to maternal vaginal or enteric microbes during birth. Instead, Caesarean-section-delivered infants are dominated by human skin and oral bacteria, including *Staphylococcus*, *Streptococcus*, *Corynebacterium*, *Veillonella*, and *Propionibacterium* [Dominguez-Bello et al., 2010; Bäckhed et al., 2015]. The gut microbiota is intimately associated with training the innate immune system, and its disruption in early life can result in infections, sepsis, and systemic immune and metabolic disorders, which influence lifelong disease risk [Zhu et al., 2015]. Microbial dysbiosis caused by Caesarean-section delivery has been associated with an increased risk of conditions such as asthma [Couzin-Frankel, 2010], obesity [Mueller et al., 2015], food allergies [Lieberman et al., 2018], type 1 diabetes (T1D) [Kostic, 2015], systemic connective tissue disorders, juvenile arthritis, inflammatory bowel disease (IBD), and leukemia [Sevelsted et al., 2015] as shown Table 1. The purpose of this review is to present the current understanding of both the microbial risk factors that increase the likelihood of a Caesarean-section delivery and the microbial dysbiosis that is thought to result from it.

Maternal Microbiome During Pregnancy

The maternal microbiota can have an impact on the course of pregnancy and potentially determine infant health outcomes. During pregnancy, the maternal body undergoes radical physiological fluctuations in hormones and immune status [Fox and Eichelberger, 2015]. Recent studies have found that these changes are concurrent with alterations in the maternal gut microbiome, with significant shifts occurring from the first to the third trimester [Koren et al., 2012]. During this period, the abundances of the phyla, Proteobacteria and Actinobacteria increases, and the overall species richness decreases [Koren et al., 2012]. However, other studies have demonstrated that the gut and oral microbiome stay relatively stable over pregnancy, while the vaginal microbiome undergoes significant changes [Bisanz et al., 2015].

Understanding the effects of microbial colonization during pregnancy is key for potential clinical applications, including risk stratification based on the maternal microbiome. Certain vaginal microbial community profiles are known to correlate with pregnancy outcomes like preterm birth [Hyman et al., 2014; Haque et al., 2017; Stout et al., 2017]. The maternal microbiome is affected by treatment with antibiotics [Bennet et al., 1986], periodontal disease [Michalowicz et al., 2006], and smoking status, and has been tied to adverse pregnancy outcomes [Paropkari et al., 2016]. While it has long been held that the inside of the amniotic sac is a sterile environment and that an infant's first microbial exposure occurs during delivery [Funkhouser and Bordenstein, 2013], recent studies have characterized bacterial DNA in amniotic fluid [DiGiulio et al., 2008], umbilical cord blood [Jiménez et al., 2005], meconium [Jiménez et al., 2008; Hu et al., 2013; Ardissone et al., 2014], and the placenta [Aagaard et al., 2014; Collado et al., 2016]. Microbiome samples from these sites yield low biomass, potentially vulnerable to contamination from other DNA sources [Kliman, 2014; Lauder et al., 2016]. Furthermore, it has been difficult to distinguish living bacterial cells from DNA products; while some reports have used culture-based techniques to quantify bacteria in placental tissues, not all placentas appeared to harbor bacteria [Stout et al., 2013]. Overall, it remains to be determined whether the presence of an intrauterine microbiota is part of a healthy and normal pregnancy. However, in several other species, such as marine sponges, domesticated chickens, and turtles, maternal microbial transmission occurs pre-birth [Funkhouser and Bordenstein, 2013]. Indeed, the identification of microbes in the meconium suggests that the fetal gut itself may be seeded with bacteria before birth [Neu, 2015]. If pre-birth maternal microbial transmission does occur in healthy pregnancies, this could have wide-ranging implications for immune development [Tamburini et al., 2016].

Causes of Caesarean Section and Confounding Factors

The host-microbiota relationship has a clear impact on health: microbial dysbiosis is known to drive a wide range of mucosal and systemic immune-mediated disorders, including IBD [Bager et al., 2012], autoimmune conditions, and allergy [Kelly et al., 2007]. However, complications that can indicate Caesarean-section delivery, such as preterm birth, extremes of maternal BMI, infection, extremes of infant size, and gestational diabetes, are often associated with microbial dysbiosis during pregnancy [Neu and Rushing, 2011]. These indications for Caesarean section may themselves have an impact on the microbiota and therefore confound our understanding of the microbiota in Caesarean-section delivery.

Preterm Birth as a Special Case

Despite improved technology and diagnosis, preterm birth (defined as <37 weeks of gestation] still represents a globally relevant epidemiological burden [Purisch and

Table 1. A non-exhaustive list of recent studies examining the association of Caesarean-section delivery with long-term health outcomes

Illness/condition	Study	Cohort characteristics	Major findings
Asthma	Thavagnanam et al., 2008	Meta-analysis of 23 studies with a sample size of 501,947	The summary risk estimates for asthma based on 23 studies was 1.22 (95% CI 1.14–1.29). In this meta-analysis, the authors observed a 20% increase in the subsequent risk of asthma in infants who had been delivered by Caesarean-section
Asthma	Huang et al., 2015	Meta-analysis of 26 studies	This meta-analysis indicates that infants born by Caesarean-section have a 16% higher risk of asthma compared to vaginally delivered infants. The risk of asthma in Caesarean-section infants is similar, independent of whether the delivery was elective or non-elective
Food allergy/ allergic rhinitis	Bager et al., 2008	Meta-analysis of 26 studies	Caesarean-section delivery was associated with an increased risk for food allergy/food atopy (OR 1.32, 95% CI 1.12–1.55; 6 studies), allergic rhinitis (OR 1.23, 95% CI 1.12–1.35; 7 studies), asthma (OR 1.18, 95% CI 1.05–1.32; 13 studies), and hospitalization for asthma (OR 1.21, 95% CI 1.12–1.31; 7 studies); whereas there was no association with inhalant atopy (OR 1.06, 95% CI 0.82–1.38; 4 studies), and eczema/ atopic dermatitis (OR 1.03, 95% CI 0.98–1.09; 6 studies)
Allergic conditions	Negele et al., 2004	2,500 infants enrolled in a German prospective multicenter birth cohort study	The authors observed that Caesarean-section delivery may be an additional risk factor for wheezing and allergic sensitization to at least food allergens up to the age of 2
Chronic immune conditions	Sevelsted et al., 2015	1.9 million children born in Denmark between ages 0 and15	Infants delivered by Caesarean-section delivery had significantly increased risk of asthma, systemic connective tissue disorders, juvenile arthritis, IBD, immune deficiencies, and leukemia. No associations were found between caesarean delivery and T1D, psoriasis, or celiac disease
Obesity	Yuan et al., 2016	Cohort study of 22,068 infants of which 4,921 were Caesarean-section deliveries	Caesarean-section-delivered infants were 15% more likely to become obese than those delivered vaginally. Additionally, Caesarean-section-delivered infants had 64% higher odds of obesity compared with their siblings that were delivered vaginally.
Obesity	Li et al., 2013	Meta-analysis of 9 studies	The pooled OR of obesity for Caesarean-section delivered infants compared with those delivered vaginally was 1.33 (95% CI 1.19–1.48)
Obesity	Darmasseelane et al., 2014	Meta-analysis of 35 studies with a sample size of 163,753	The authors observed an average increase in BMI of almost 0.5 kg/m^2 in Caesarean-section-delivered infants compared to those delivered vaginally, and increased odds of overweight and obesity (>20%)
IBD	Bager et al., 2008	A register-based national cohort study of 2.1 million Danish children born between 1973 and 2008	Caesarean-section delivery was associated with moderately, yet significantly, increased risk of IBD at age 0–14 (IRR 1.29, 95% CI 1.11–1.49), regardless of parental disposition to IBD

Table 1 (continued)

Illness/condition	Study	Cohort characteristics	Major findings
IBD	Bernstein et al., 2016	1,671 individuals with IBD and 10,488 controls	Overall, there was no difference in the percentage of IBD cases born by Caesarean-section (11.6%) vs. controls (11.7%, $p = 0.93$). In a multivariate analysis, Caesarean-section delivery was not associated with an increased risk of subsequent IBD, controlling for age, Gender, urban residence, and income (OR 1.04; 95% CI 0.89–1.23)
T1D	Cardwell et al., 2008	Meta-analysis of 20 studies with a sample size of 2,133,236	This analysis demonstrated a 20% increase in the risk of childhood-onset T1D after Caesarean-section delivery
T1D	Bonifacio et al., 2011	1,650 infants born to parents with T1D	Caesarean-section-delivered infants ($n = 495$) had a more than twofold higher risk for T1D than those delivered vaginally (HR 2.5; 95% CI 1.4–4.3; $p = 0.001$). Caesarean-section did not increase the risk for islet autoantibodies ($p = 0.6$) but was associated with a faster progression to T1D after the appearance of autoimmunity ($p = 0.015$)
T1D	Stene et al., 2003	A total of 1,382,602 individuals with 1,863 cases of T1D	Caesarean section was not associated with T1D
T1D	Clausen et al., 2016	858,201 singleton births with 1,503 cases of T1D	Broad-spectrum antibiotics was associated with an increased rate of T1D in infants delivered by either intrapartum caesarean section (HR 1.70; 95% CI 1.15–2.51) or pre-labor Caesarean section (HR 1.63; 95% CI 1.11–2.39), but not in vaginally delivered infants

IBD, inflammatory bowel diseases; T1D, type 1 diabetes; HR, hazard ratio; IRR, incidence rate ratios.

Gyamfi-Bannerman, 2017]. In the United States alone, preterm delivery accounts for about 1 in 10 births and these infants are more likely to be delivered by Caesarean section [Racusin et al., 2016]. This reduces their exposure to maternal vaginal and enteric microbes, and results in differential immune system development, which can shape microbial colonization in their already immature guts.

In addition, they are subject to higher rates of formula feeding [Madan et al., 2016], invasive procedures, antibiotics [Yassour et al., 2016], and other medications that alter gastrointestinal pH, all of which contribute to the altered assembly of the microbial community [Donders et al., 2010]. Finally, preterm infants with extended stays in the neonatal intensive care unit (NICU) are dominated by microbes associated with the NICU environment, many of which harbor antibiotic resistance genes [Brooks et al., 2014].

No single cause of preterm birth has been identified, but many of the risk factors involve microbial dysbiosis, including ascending urogenital infections [Goldenberg et al., 2008], descending periodontal infections [Michalowicz et al., 2006], and abnormal vaginal microbiota [Donders et al., 2010].

As mentioned above, the literature suggests significant differences in the vaginal microbiome from women with term and preterm delivery outcomes, implying potential diagnostic relevance [Haque et al., 2017]. Furthermore, epidemiologic studies have established a correlation between oral flora, periodontal disease, and preterm birth [Michalowicz et al., 2006]. Research from Hällström et al. [Hällström et al., 2004] found a link between altered intestinal colonization and Caesarean-section delivery in preterm infants, and also identified changes in fecal microbiota with the onset of necrotizing enterocolitis. Although preterm infants represent a significant fraction of Caesarean-section-delivered infants, there are many confounding factors and for the purposes of this review, we will consider only full-term Caesarean-section-delivered infants.

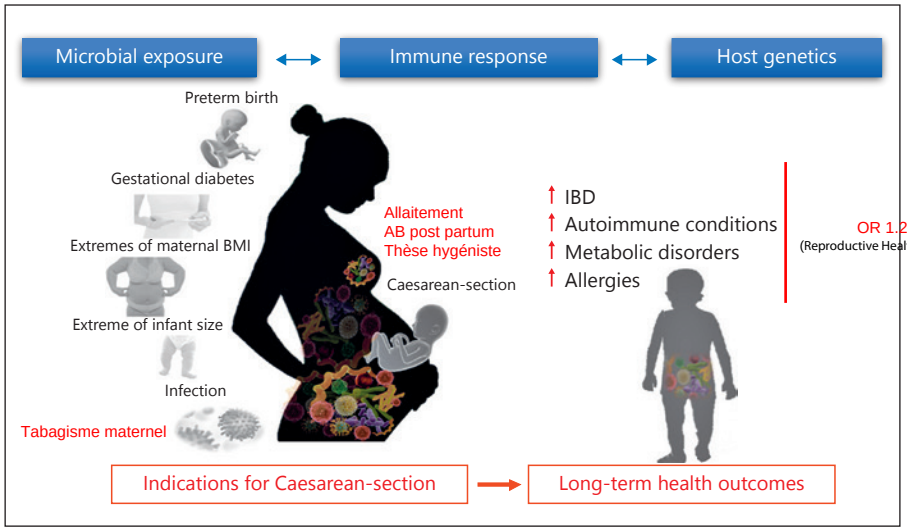

Fig. 1. A summary of our current understanding of factors that indicate and conditions linked with a Caesarean-section delivery. The developing gut microbiota, microbial exposures from the environment, and host genetics interact to mediate infant immune responses. Several indicators of Caesarean-section, including preterm birth, extremes of maternal body mass index (BMI), infection, extremes of infant size, and gestational diabetes, may independently cause microbial dysbiosis and confound our understanding of the effects of Caesarean-section. Microbial dysbiosis caused by Caesarean-section delivery is linked with an increased risk for inflammatory bowel disease (IBD) and a wide range of autoimmune, allergic, and metabolic conditions.

Other Confounding Conditions

Other conditions that result in increased rates of Caesarean-section delivery include extremes of maternal BMI, infection, gestational diabetes, and infant size. High maternal BMI is not solely attributable to genetic factors but also microbial composition [Zhu et al., 2015]. Gut microbial dysbiosis can affect nutrient absorption, inflammation, and microbial translocation, as well as fetal gut colonization and development of fetal metabolic tissues [Gohir et al., 2014]. During pregnancy, women are in an altered immune state and therefore more susceptible to pathogens, such as human immunodeficiency virus [Yee et al., 2018], hepatitis C [Yi et al., 2018], Zika virus [Magnani et al., 2018], *Listeria monocytogenes*, *Plasmodium* spp., influenza viruses, *Chlamydia trachomatis*, Group B *Streptococcus*, *Treponema pallidum*, and herpes viruses [Guo et al., 2018]. These pathogens can cause severe syndromes, depending on the timing of infection during pregnancy [Vermillion and Klein, 2018]. For example, cytomegalovirus is the most common congenital infection worldwide, and direct infection of the fetus can lead to neurosensory deficits, learning disabilities, microcephaly, and psychiatric disorders [Racicot and Mor, 2017]. When cytomegalovirus is latent or reactivated in the mother, even without directly infecting the fetus, it can lead to fetal growth restriction, spontaneous pregnancy loss, or preeclampsia, all symptoms of early placental insufficiency [Racicot and Mor, 2017]. Notably, while these conditions are known to perturb the maternal microbiota and increase the likelihood of Caesarean-section delivery, they may additionally have microbially mediated health effects on the infant, independent of the mode of delivery.

Caesarean-Section and Long-Term Health Outcomes

As mentioned previously, the human microbiota can have an impact on pregnancy and childhood health. In particular, the infant microbiota and therefore Caesarean-section-related dysbiosis may play a role in long-term health outcomes as shown in Figure 1. Although the infant microbiota has been studied across multiple body sites, the bulk of the literature and the main focus of our review deals with the microbiota of the infant gut and immune responses to microbial exposure.

Immune and Metabolic Health

Recently, the role of the gut microbiota has been appreciated as essential to immune and metabolic development in early life. In Caesarean-section-delivered infants, typical mother-to-infant microbial transmission is disrupted, so this immune and metabolic development is altered [Sevelsted et al., 2015a]. This has important ramifications for long-term immune-mediated health outcomes: Caesarean-section-delivered infants have increased the incidence of T1D, IBD, and autoimmune/allergic conditions [Kelly et al., 2007].

Kostic Kostic, 2015 studied the dynamics of the human infant gut microbiome in the progression of T1D in a cohort of 33 Finnish and Estonian infants genetically predisposed to T1D. While they noted great variation in the overall taxonomic composition between and within infants over time, there was significantly less variation in the metabolic potential of the microbiome. They also observed a drop in species richness, alterations in proinflammatory gene functions, and alterations in levels of

serum and stool metabolites in infants who progressed to T1D. The trends they observed that distinguished T1D progressors from nonprogressors may have potential diagnostic applications [Kostic, 2015]. Additionally, other studies also suggested that the pathogenesis and clinical course of T1D result from the interplay between genetic susceptibility, early life environmental exposures, and the innate immune response [Vehik and Dabelea, 2012].

The impact of Caesarean section on immune-related diseases is still a nascent area of research. However, another study examined a cohort of 2 million Danish children delivered at term between 1997 and 2012 and identified Caesarean-section delivery as a risk factor for immune-related diseases including asthma, systemic connective tissue disorders, juvenile arthritis, IBD, immune deficiencies, and leukemia [Sevelsted et al., 2015a]. The results imply that early life events may dictate immune abnormalities that increase risk for diseases later in life.

Gastrointestinal Tract Outcomes

Antibiotics are widely used during pregnancy and prior to and immediately preceding Caesarean-section delivery to prevent infection. However, non-culture-based studies of the adult intestinal microbiome show that antibiotic exposure may perturb the gastrointestinal tract microbiota for years [Murgas Torrazza and Neu, 2011]. Moreover, increasing rates of antibiotic resistance in children can lead to infections and gut dysbiosis [Medernach and Logan, 2018].

Microbial perturbations in the gastrointestinal tract have been associated with Crohn's disease. In a Danish national cohort study of 2.1 million people born during 1973–2008, a total of 8,142 were diagnosed with IBD before the age of 36. Controlling for genetic disposition to IBD, the major factor associated with increased risk of IBD was Caesarean-section delivery. Furthermore, the majority of the IBD diagnoses occurred after age 15, implying that dysbiosis from Caesarean-section delivery at the beginning of life may have lifelong health implications [Bager et al., 2012].

Risk of Atopy and Allergic Disease

Food allergy is a global public health problem, affecting up to 8% of children and up to 5% of adults in the United States, the United Kingdom, Canada, and Australia. While the drivers of allergic diseases remain unclear, evidence points to gene-environment interactions beginning in early development [Lieberman et al., 2018]. In particular, Caesarean-section delivery has been shown to increase food allergy [Dominguez-Bello et al., 2016]. Furthermore, an infant's odds of developing allergy is influenced by the feeding mode (breast milk or formula), which represents the first nutrition-related microbes entering the human body [Cabrera-Rubio et al., 2012]. The feeding mode therefore plays an important role in exposure to and response to food allergens in early development. Bager et al. [Bager et al., 2008] performed a meta-analysis on 26 studies to identify the association of Caesarean-section delivery with the risk of atopy and allergic disease. They concluded that Caesarean section increased the risk for allergic rhinitis, asthma, hospitalization for asthma, and perhaps food allergy/food atopy but did not affect the risk of inhalant atopy or atopic dermatitis.

Metabolic Syndrome

Maternal BMI may be a determinant of the infant gut microbial community over lactation. Studies have shown that breast milk from obese mothers tends to contain a distinct and less diverse microbial community compared with milk from normal-weight mothers [Cabrera-Rubio et al., 2012]. The breast milk microbiota also differs between mothers who delivered by Caesarean section vs. vaginally, which could be due to the surgery or the presence of physiological stress or hormonal signals. As breast milk represents one of most important postpartum sources of mother-to-infant microbial transmission, further work is necessary to quantify the impact of the breast milk microbiota on the infant's gut. The Northern Manhattan Mothers and Children Study followed 436 mother-child dyads until age 7 to examine the effect of maternal use of antibiotics in the second or third trimester of pregnancy. The results showed that children exposed to antibiotics during the second or third trimesters had 84% higher risk of obesity. Caesarean-section delivery was independently associated with 46% greater risk for childhood obesity, independent of antibiotic use and independent of whether the Caesarean section was elective or non-elective [Mueller et al., 2015].

Microbiota Restoration Therapies for Infants

A perturbed infant gut microbiota may be returned to a baseline state through the reintroduction of commensal bacteria along with breastfeeding and/or through pre/probiotic formulations [Neut et al., 1987; Azad et al., 2013]. However, the US Food and Drug Administration is yet to approve any pre/probiotic formulations to treat microbial dysbiosis caused by Caesarean-section deliv-

ery. That said, an ongoing clinical trial in the United Kingdom (clinical ID: ISRCTN11690200) will investigate whether short-term daily probiotic supplementation with *Bifidobacterium infantis* in breastfed babies delivered by Caesarean section promotes a healthy fecal microbiota that can be maintained with breastfeeding until weaning at 6 months ["ISRCTN – ISRCTN11690200, 2018].

Likewise, a growing number of US Food and Drug Administration trials are testing the safety and efficacy of pre/probiotics that target illnesses associated with Caesarean-section delivery. One example is a recent trial of early-life supplementation with *Lactobacillus rhamnosus GG* in infants at high risk for asthma. The supplementation promoted subtle yet important taxonomic and metabolic remodeling in the infant gut, and Durack et al. [Durack et al., 2018] observed an increase in the number of regulatory T cells ex vivo at 6 months of age, providing evidence for immunomodulation. It should be noted that this supplementation's efficacy in asthma prevention is yet to be determined.

Another strategy to restore a healthy microbiota is called "vaginal seeding," exposing Caesarean-section-delivered infants to maternal vaginal contents [Braegger et al., 2011]. Recent results suggest that the fecal, skin, and oral microbiome of seeded infants more closely resemble those of vaginally delivered than Caesarean-section-delivered infants [Dominguez-Bello et al., 2010]. Although the efficacy and long-term health consequences of vaginal seeding remain unclear, these results demonstrate that maternally transmitted vaginal microbes can be partially restored at birth in Caesarean-section-delivered infants. While this strategy is limited, as it does not expose the infant to maternal enteric contents, it sets the stage for the development of novel microbial therapies and/or small molecules for restoring the composition and development of a healthy infant microbiota.

Overall, the association between microbial dysbiosis in infants delivered by Caesarean section and long-term health outcomes is a new field of research. Going forward, it will be necessary to elucidate mechanisms involved, such as metabolic and immune pathways and microbial function, in order to apply this research to personalized microbiome-based therapies.

Disclosure Statement

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