Feature Article

Intervention strategies for cesarean section–induced alterations in the microbiota-gut-brain axis

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Microbial colonization of the gastrointestinal tract is an essential process that modulates host physiology and immunity. Recently, researchers have begun to understand how and when these microorganisms colonize the gut and the early-life factors that impact their natural ecological establishment. The vertical transmission of maternal microbes to the offspring is a critical factor for host immune and metabolic development. Increasing evidence also points to a role in the wiring of the gut-brain axis. This process may be altered by various factors such as mode of delivery, gestational age at birth, the use of antibiotics in early life, infant feeding, and hygiene practices. In fact, these early exposures that impact the intestinal microbiota have been associated with the development of diseases such as obesity, type 1 diabetes, asthma, allergies, and even neurodevelopmental disorders. The present review summarizes the impact of cesarean birth on the gut microbiome and the health status of the developing infant and discusses possible preventative and restorative strategies to compensate for early-life microbial perturbations.

INTRODUCTION

Humans share a mutualistic relationship with the complex community of microbes living in their bodies, collectively known as the microbiota. The microbiota is well known to play a critical role in the development and later function of the gastrointestinal,[1] metabolic,[2] and immune systems.[3,4] There is now a growing body of evidence that suggests the gut microbiota also influences the brain and behavior.[5–10] Robust preclinical and clinical findings indicate that a bidirectional route of communication exists between the brain and the gut microbiota and this is termed the microbiota-gut-brain axis (for detailed description of this axis in health and disease across the lifespan, see recent reviews[5,11–15]).

The exact mechanisms by which the gut microbiota communicates with the brain are not yet clear; however, they include immunological, endocrine, metabolic, and neural pathways (for detailed discussion of pathways of communications, see recent reviews[7,9,16–18]). Although immune signaling through the production of cytokines is an important route of communication between the gut and the brain, it is not involved in all conditions. For example, subclinical infection by pathogenic

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bacteria fails to induce a change in cytokine release, yet it alters behavior and central nervous system (CNS) neurochemistry.[19] However, it is clear that mice raised without exposure to microorganisms (ie, germ-free mice[GF]) have underdeveloped adaptive and innate immune systems.[20,21] The biochemical complexity of the gut is even greater than that of the brain.[16,22] Indeed, many of the hormones produced by the gut microbiota also act as neurotransmitters within the CNS, including catecholamines, gamma-aminobutyric acid, serotonin, glutamate, histamine, acetylcholine, and tryptophan.[20,23] These metabolic compounds have bioactive properties and can be transported throughout the entire body via the circulatory system.[24] Of particular note is tryptophan, an essential amino acid and a precursor of many biologically active agents, including the neurotransmitter serotonin.[25] A growing body of evidence points to dysregulation of the often-overlooked kynurenine arm of the tryptophan metabolic pathway in many disorders of both the brain and the gastrointestinal tract.[25,26] Another important signaling aspect of microbiota-to-brain signaling is the hypothalamus-pituitary-adrenal axis, which regulates cortisol secretion. Cortisol can affect immune cells both locally in the gut and systemically. Cortisol can also alter gut permeability and barrier function and change gut microbiota composition.[7] In addition, microbes can impact the responsivity of the hypothalamic-pituitary-adrenal axis, as seen in several studies demonstrating that neuroendocrine signaling is altered in response to microbial manipulation.[27–30]

Given that the human gut is heavily innervated,[31,32] it is not surprising that neural pathways represent another important route connecting the brain and the gut. The involvement of the vagus nerve in bottom-up microbiota-gut-brain communication appears to be dependent on the bacterial strain under investigation: Some studies have found that the vagus nerve is necessary for communication to the brain,[19,28,33] while others have documented vagus-independent effects.[34,35] The enteric nervous system is also responsive to microbial interventions. Both potential probiotic treatment and the absence of bacteria can alter the excitability of enteric nervous system sensory neurons.[36,37] Together, these findings indicate there are likely numerous systems simultaneously involved in the bidirectional transfer of information between the brain and the gut.

ALTERED MICROBIOTA COMPOSITION IN PERINATAL PERIOD, NEURODEVELOPMENT, AND HEALTH

A number of diverse factors can contribute to mammalian gut microbiota content and complexity, and the progression of bacterial colonization is not random.[38] Over the last few centuries, especially in the industrialized world, increases in births by cesarean (C)-section, prematurity rates, and the use of antibiotics in pregnancy, in addition to changes in infant feeding, living conditions, diet, lifestyle, and general hygiene may have altered the ways in which enteric microbial communities are acquired.[39,40,180] These microbial alterations have been suggested to correlate with a variety of immune (eg, asthma) and metabolic (eg, childhood obesity) disorders.[41,42] However, the causal relationship between C-sections and such interactions is less studied.

One of the first and most important developmental windows is the post birth neonatal period. The exposure to bacteria during birth is a critical juncture in the establishment of a stable core gut microbiota.[43,44] The effects of the intestinal microbiota on brain physiology include synaptogenesis, regulation of microglia development and maturation, and regulation of neurotransmitters and neurotrophic factors such as brain-derived neurotrophic factor.[27,29,30,45–47]

Recently, several preclinical studies using GF mice have highlighted the ability of early-life microbiota to influence neurodevelopment, with long-lasting effects on neural function.[27,29,30,45,48] During development, the nervous system is assembled and sculpted by a series of temporally regulated developmental processes that shape the functional neural circuitry, which is critical for normal cognitive, motor, and emotional development. This is a complex process consisting of an orchestrated series of neurodevelopmental events including, but not limited to, neurogenesis (the birth of new neurons), axonal and dendritic growth, synaptogenesis, and refinement of these synaptic connections, which generate the required numbers of neurons and the appropriate synaptic density to match the requirements of the neural circuit they become part of, a process known as systems matching.[49,50] These developmental processes begin in utero and are later refined and modified during early postnatal development. A large body of scientific evidence indicates that the first 1000 days – from conception until a child's second birthday – is the most critical time for a positive impact on a child's cognitive development.[43,51] Maternally derived environmental disturbances (eg, infection, stress, drug and alcohol exposure, preterm birth) during this time period can have profound and enduring structural and functional consequences for brain development in affected offspring.[52–55]

Despite the overwhelming evidence of the crucial role that the microbiota plays in the postnatal development and maturation of the CNS, the pathways as to how disturbances in microbiota development could lead to abnormal brain development, cognitive and behavioral deficits, allergy/autoimmunity, and metabolic disorders remain to be elucidated (Figure 1). Importantly, a recent study has provided one potential

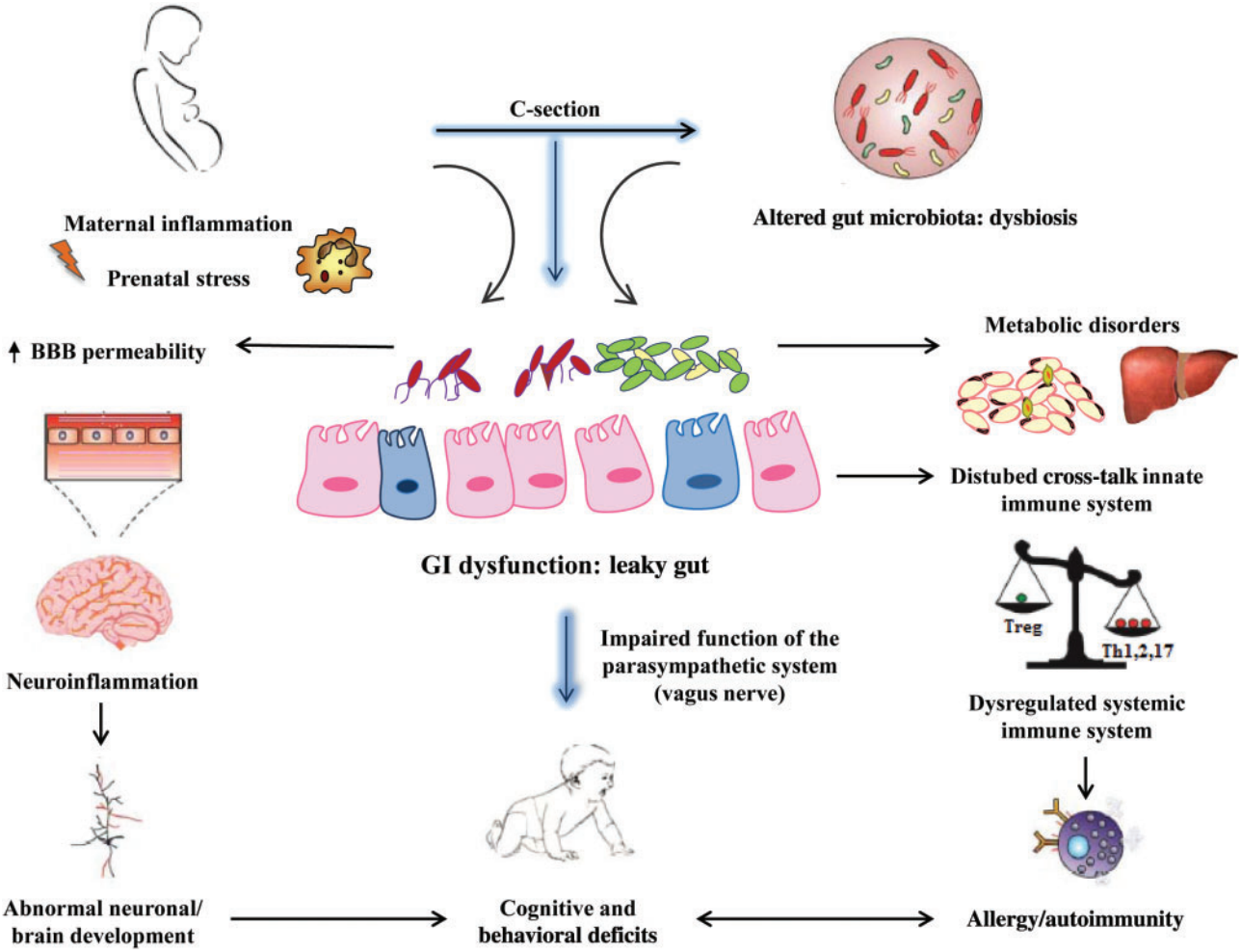

Figure 1 **Cesarean section can alter colonization of the newborn intestine, which is a critical event influencing many developmental and physiological processes and, thereby, the functioning of the immune and neuroendocrine systems, with long-lasting effects on health.** It is thought that an unhealthy microbiota can promote the increased translocation of pathogenic bacterial components from the intestinal mucosa to the systemic circulation, where they activate innate immunity characterized by production of proinflammatory cytokines, resulting in metabolic inflammation and abnormal gut function. *Abbreviation:* BBB, blood-brain barrier.

signaling mechanism involving the blood-brain barrier (BBB) through which the microbiota may modulate brain function during development.[56] It is now becoming more apparent that intestinal microbiota-brain communication is initiated during gestation and propagated throughout life. The BBB ensures an optimal microenvironment for neuronal growth and development.[57] An intact and regulated BBB is essential for protecting neonates during the critical periods of neurodevelopment.[58,59] Increased BBB permeability has been associated with cytokine infiltration and neuroinflammation, resulting in abnormal neuronal development and disrupted immune priming, leading to neurodevelopmental, immune, and autoimmune disorders.[60]

The mammalian lifespan can be arbitrarily divided into 5 stages – infancy, adolescence, adulthood, middle age, and old age – based on a variety of physiological and psychological parameters.[61] Studies in GF mice have demonstrated that critical time windows exist during which certain deficits of the microbiota-gut-brain axis are amenable to microbial intervention. For example, the enhanced hypothalamic-pituitary-adrenal axis response of GF mice was partly corrected by reconstitution with specific pathogen-free microbiota at an early stage, but not by colonization exerted at a later stage.[27] This indicates the existence of a critical window in early adolescence (in rodents, adolescence is generally thought to be the period between postnatal day 21 and postnatal day 60)[61] during which the CNS is still sensitive to the microbial signals involved in normal hypothalamic-pituitary-adrenal axis development. Bacterial colonization at the post-weaning stage also normalizes alterations in anxiety-like behavior, microglial homeostasis, and BBB permeability in GF mice.[30,46,56] Moreover, it has been shown that dietary

administration of short-chain fatty acids, microbiota-derived metabolites, or the bacteria that produce them can reverse alterations in microglia homeostasis and the BBB permeability observed in GF mice.[46,56] However, some microbial-based alterations appear to be permanent. For example, colonization of GF mice at the post-weaning stage does not normalize changes in hippocampal neurogenesis and central levels of serotonin.[30,62] Colonization post weaning also only restores certain aspects of the social deficits in GF mice, ie, social preference is normalized, but social cognition is unaffected.[48] These data suggest that the gut microbiota is capable of modulating brain development and behavior, but that critical time windows exist for intestinal microbes to exert this influence.

Alteration to the composition of the gut microbiota often occurs during the postnatal period. The use of antibiotics and feeding regime (whether breast fed or formula fed) can have a tremendous impact on the development and complexity of the microbiota,[63] as well as influencing neural development.[64] C-section birth has recently been suggested as another way in which this microbial alteration is occurring. While medically-necessary C-sections occur in 10% to 15% of pregnancies worldwide,[65,66] the number of elective surgeries has increased over the last few decades. For example, in the United States approximately 1 in 3 babies was delivered via C-section in 2013, while in Northern European countries rates of C-section births are lower.[67] In other regions, such as parts of Brazil and China, C-section rates are skyrocketing for cultural,[68] cosmetic, and healthcare reasons rather than medical reasons.[69] Moreover, it is worth noting that some extreme socioeconomic disparities exist, which limit the access to C-section delivery (especially in sub-Saharan Africa).[70] However, despite these cultural differences, accumulating data suggests that in order to improve maternal and perinatal results, C-sections should only be performed when there is a medical indication.[71]

Disrupting the mother-to-newborn bacterial transmission by C-section delivery may increase the risk of disease in later life. For example, early-life microbiota perturbations, such as low levels of *Bifidobacterium,* have been reported to precede the development of certain disorders such as allergy and obesity.[72–75] Indeed, C-section delivery has been associated with an increased risk of celiac disease,[76] asthma,[77,78] type 1 diabetes,[79] and obesity.[80,81] The available clinical association data for C-section delivery are summarized in Table 1. It should be noted that most of the evidence is association based, and clear evidence of causality of microbiome changes to functional outcomes have not been proven.

Importantly, recent epidemiological findings suggest that C-section delivery is associated with a modest increase of some neuropsychiatric disorders such as bipolar disorder, autism spectrum disorders, and attention deficit hyperactivity disorder.[93,94] However, other more definitive studies have not found an association between mode of delivery and autism or attention deficit/hyperactivity disorder or psychosis.[95,96] More recently, an increased risk for obsessive compulsive disorder was associated with a variety of perinatal risk factors including birth by C-section, even after controlling for shared familial confounders and measured covariates (including sex, year of birth, maternal and paternal age at birth, and parity). Nevertheless, further studies are needed to determine whether C-section delivery is causally associated with autoimmune, metabolic, and neuropsychiatric diseases.[97]

The disruption of the normal maturation of the microbiota-brain-gut axis by C-section could, therefore, alter developmental trajectories and may lead to the onset of neurodevelopmental and other brain disorders later in life.[5–10,43,98] The exposure to bacteria during birth is a critical event in the establishment of stable core gut microbiota, which is altered when infants are delivered via C-section. In fact, the microbiome of infants born vaginally most closely resembles that of the mother's vagina and feces[44] and is rich in beneficial bacteria such as *Bifidobacterium longum* subsp. *infantis* and Bacteroidetes.[38,99] In contrast, the microbiome of infants born via C-section is more similar to the hospital environment and to the mother's skin (eg, *Staphylococcus, Corynebacterium, Propionibacterium* spp.).[44,100]

STRATEGIES INVOLVED IN POSITIVELY SHAPING THE GUT MICROBIOTA AFTER C-SECTION

As mentioned above, the microbial composition of infants delivered by C-section differs from those born vaginally.[44] The importance of the composition of the gastrointestinal microbiome in health (including brain health), particularly during early life, indicates that microbial-based interventions could represent effective strategies for targeting these potential negative health outcomes. Summarized here are the possible strategies that may be used to introduce a healthy balance of commensal gut microbiota. Many of these approaches have already been implicated in the improvement of microbial colonization of the gut in early childhood and may, thus, be associated with health benefits (Figure 2).

Vaginal seeding

The inoculation of a neonate with maternal vaginal microbiota immediately following C-section delivery is known as vaginal seeding. As previously mentioned, the

Table 1 **Summary of the impact of C-section on newborn health**

System	Effects	Specific changes	Specific changes in health condition/disorder/dysbiosis	Role of microbiota	Type of study	Reference
Immune system dysregulation	Allergy	Allergic rhinitis and peripheral blood eosinophilia	Inverse association of bacterial diversity in the early intestinal flora 1 and 12 mo after birth with the risk of allergic sensitization (serum-specific IgE; peripheral blood eosinophils and allergic rhinitis)	Reduced bacterial diversity of the infants' intestinal flora associated with an increased risk of allergic sensitization, allergic rhinitis, and peripheral blood eosinophilia	Clinical Clinical	Bisgaard et al. (2011)[82] Watanabe et al. (2003)[72]
		Atopic dermatitis	Low prevalence of *Bacteroides* and *Bifidobacterium* spp. associated with atopic dermatitis	Percentages of *Bifidobacterium* significantly lower in patients with severe skin symptoms *Staphylococcus* significantly higher in patients with atopic dermatitis		
	Asthma "Hygiene hypothesis"	Chronic inflammatory disease of the airways	Increased risk of asthma and atopy in children born by C-section; demonstrated using a combination of 2 methods: 1) evaluation of registers and questionnaire (symptoms in the child and the family) and 2) clinical examination (delivery history and general pediatric clinical examination) Higher risk of asthma in children born by C-section than those born by vaginal delivery, particularly the children of allergic parents Protection from development of allergic illnesses may be conferred by infections and unhygienic contacts	Decline of infections in Western countries coincides with the origin of increased incidence of autoimmune and allergic diseases Toll-like receptor stimulation can recapitulate the protective effect of infectious agents on allergy and autoimmunity Rise in reported allergy symptoms is not due to being too clean, but losing touch with "old friends"	Clinical Clinical Clinical and preclinical evidences	Kero et al. (2002)[78] Roduit et al. (2009)[83] von Mutius (2007)[84]
	Autoimmune diseases	Type 1 diabetes	Risk of diabetes increased by late preterm birth (34–36 wk) and C-section delivery Higher risk of diabetes in offspring associated with increased maternal age 20% higher risk of childhood-onset type 1 diabetes after C-section delivery (from a meta-analysis of observational studies)Autoimmunity prevented by parenteral	Probiotics that stimulate TLRs also protect from autoimmune diseases Microbiota development in infants is affected by mode of delivery and relates	Clinical Clinical Preclinical (mouse) Clinical Systematic review and meta-analysis of observational studies Clinical Clinical	Algert et al. (2009)[79] Cardwell et al. (2008)[85] Aumeunier et al. (2010)[86] Mezoff et al. (2013)[87] Akobeng et al. (2006)[88] Marild et al. (2012)[76] Jakobsson et al. (2014)[89]

(continued)

Table 1 **Continued**

System	Effects	Specific changes	Specific changes in health condition/disorder/dysbiosis	Role of microbiota	Type of study	Reference
			administration of multiple TLR agonists TLR-mediated effects involve immunoregulatory cytokines such as IL-10 and transforming growth factor-beta and different subsets of regulatory T cells Increased risk of immunoglobulin E-mediated food allergy associated with C-section delivery	differences in colonization patterns to the maturation of a balanced Th1/Th2 immune response	Preclinical (mouse) Clinical Systematic review and meta-analysis	Hansen et al. (2014)[90] Sevelsted et al. (2015)[91] Li et al. (2014)[92]
		Celiac disease	Protection from celiac disease associated with breastfeeding Celiac disease later in life positively associated with elective, but not emergency, cesarean delivery			
	Low levels of Th1 response and effects on the regulatory immune system Inflammatory bowel disease		Lower total diversity of the microbiota in C-section compared with vaginally delivered infants throughout the first 2 years of life Lower diversity of the phylum Bacteroidetes in C-section-born infants during the first 2 years of life Increased circulating levels of Th1-associated chemokines during infancy (CXCL10 and CXCL11 in blood) associated with vaginal delivery Lower proportions of regulatory T cells, tolerogenic dendritic cells, and less IL-10 gene expression in mesenteric lymph nodes and spleens of C-section-born adult mice Several chronic immune diseases associated with cesarean delivery as an early-life environmental risk factor			

(continued)

Table 1 **Continued**

System	Effects	Specific changes	Specific changes in health condition/disorder/dysbiosis	Role of microbiota	Type of study	Reference
			Increased risk of inflammatory bowel disease with cesarean delivery			
Metabolic dysregulation	Obesity		Increased risk of childhood obesity in infants delivered by C-section, even after adjusting for maternal body mass index, birth weight, and other variables (prospective prebirth cohort study) Increased body mass in childhood and adolescence associated with cesarean delivery (longitudinal birth cohort study, following subjects up to 15 years of age) Higher numbers of bifidobacteria in fecal samples during infancy in children who remained at a normal weight than in children who became overweight Greater number of *Staphylococcus aureus* and microbiota aberrancy during infancy in children who became overweight than in children who were normal weight Fecal microbiota of C-section infants was dominated with *Citrobacter* sp., *Escherichia coli,* and *Clostridium difficile* while the most abundant bacterial species in vaginally delivered infants were *Acinetobacter* sp., *Bifidobacterium* sp., and *Staphylococcus* sp. Intestinal microbiota of C-section-delivered infants also characterized by an absence of *Bifidobacteria* species in this study[75]	Deviations in gut microbiota may predispose to energy storage and obesity; therefore, early microbial differences may predict weight later in life Aberrant compositional development of the gut microbiota precedes becoming overweight. The large load of *E. coli* in C-section-delivered babies in comparison with vaginally delivered counterparts again points toward the aberrant and disturbed gut microbial community structure in these infants	Clinical (prospective prebirth cohort study) Clinical (longitudinal birth cohort study) Clinical Clinical	Huh et al. (2012)[80] Blustein et al. (2013)[81] Kalliomaki et al. (2008)[74] Pandey et al. (2012)[75]

Abbreviations: C-section, cesarean section; IL, interleukin; TLR, toll-like receptor.

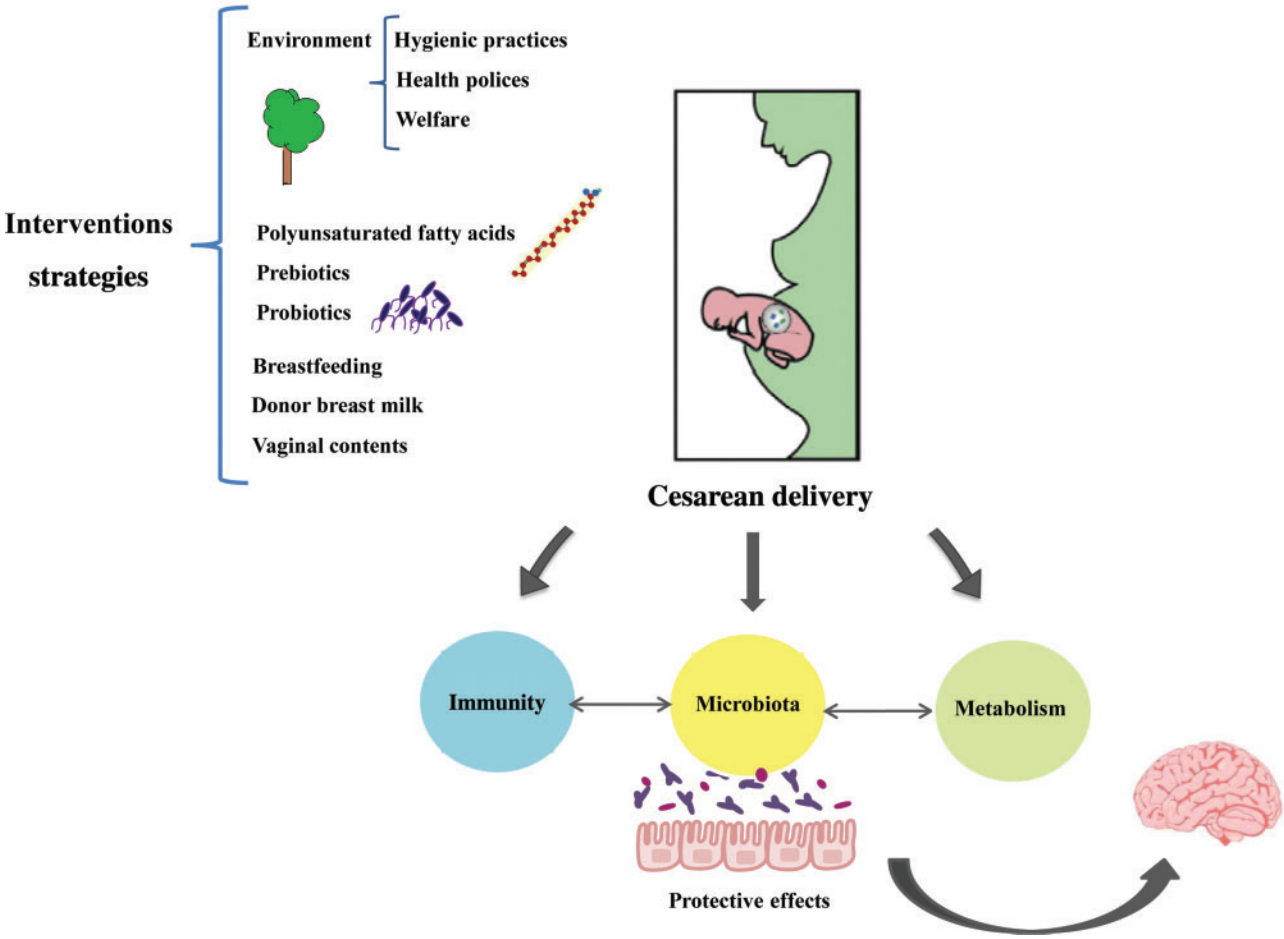

Figure 2 **Schematic representation of the main strategic points of intervention to reverse the effects of cesarean section delivery.** This can be done by improving the environment through different hygienic habits and health practices. Alternatively, the intervention could be focused on the mother herself by using probiotics and/or prebiotics and/or polyunsaturated fatty acids during pregnancy. Finally, the intervention could focus on the newborn with "seeding" approaches: breastfeeding instead of formula feeding or the use of infant formulas enriched and improved with probiotics/prebiotics. This figure summarizes the current modulating therapies to improve the composition of the microbiota and neurodevelopmental health of the infant.

composition of the microbiota in early life is strongly influenced by mode of delivery,[44] which could account for the increased risk of certain diseases associated with C-section delivery. Therefore, vaginal seeding is a potential way to colonize C-section infants with the microbes they would have received had they been delivered vaginally.[101]

Recently, Dominguez-Bello et al.[101] published results of the first pilot study demonstrating that vaginal seeding could successfully colonize C-section infants with vaginal bacteria. Two minutes after birth, C-section-delivered infants were swabbed with vaginal fluid over their entire bodies. Similar to vaginally delivered babies, the gut, oral cavity, and skin of seeded newborns were enriched with vaginal microbes for the first 30 days of life. Despite these findings, the study has some considerable drawbacks: most notably, only 4 babies were included in the study and the microbiome analysis was only conducted for 30 days following birth. The authors stress, however, that this was a proof-of-principle experiment and that reproduction in a larger cohort with a longer follow-up period is necessary.

Vaginal seeding has continued to garner increasing attention in the media, as well as curiosity from expectant mothers. Noticing this trend, Cunnington et al.[102] published an editorial in the *British Medical Journal* focusing on the risks of the approach and cautioning against its unsupervised usage. The authors argue that there is not yet conclusive evidence proving that vaginal seeding is beneficial to the child. In fact, by performing this procedure, parents could unknowingly infect their child with pathogens present in vaginal fluid, which the mothers may carry asymptomatically. The authors are mostly concerned about accidental infection with group B. *Streptococcus*, which is the most common cause of neonatal sepsis and is carried by 20% to 30% of

pregnant women.[103,104] Finally, the authors caution that more studies are needed to demonstrate if the benefits are worth the potential risks and if parents do choose to perform vaginal seeding, they are advised to disclose this information to their healthcare providers.

In response to Cunnington et al.[102] Knight and Gilbert[105] published an editorial in support of vaginal seeding. Therein, they present the multitude of health-related dilemmas parents face on a daily basis for which there is no clear, evidence-based right or wrong decision. The authors argue that vaginal seeding does indeed modify the infant's microbiome,[101] while also admitting that the procedure may not ultimately improve clinical endpoints. As for the risk of infection, the authors recommend that mothers be screened for group B. *Streptococcus* and other pathogens before vaginal seeding is performed. It is worth noting that all pregnant women in Canada and the United States are offered group B. *Streptococcus* screening[106,107] but this is not universally offered to pregnant women in the United Kingdom and Ireland.[108] In conclusion, the authors stress that in both life and science it is necessary to make decisions before all the evidence is available.

Vaginal seeding is a promising, albeit controversial, approach to the colonization of C-section-delivered babies with vaginal microbes. However, it is clear that further research is necessary to determine the efficacy and safety of the procedure. Thus, targeted nutritional or environmental interventions may represent the best strategy to compensate for early-life microbial perturbations in the meantime, and these are described below.

Microbial environment

Epidemiological evidence indicates that exposure to "green spaces" rapidly induces positive changes to our psychological, physiological, and endocrine systems. These effects could be due to the bacteria found in green spaces as numerous studies now report that microbial exposure has beneficial outcomes.[40,109] The biodiversity of the child's environment, including family members who have contact with the baby and hygienic practices (eg, cleaning of baby's soother through sucking or by other methods), can directly impact the diversity of microbes that are transferred to the infant. Indeed, the "old friends" hypothesis posits that a diverse community of symbiotic microorganisms is necessary to maintain optimal health.[40,109] Diminished exposure to such microbes, which evolved together with the human organism both within the microbiota and in the environment, during the perinatal period may cause immunoregulatory and psychosocial deficits.[109] Infants delivered by C-section have an altered microbial composition and reduced bacterial diversity, and this mode of delivery is associated with increased risk of developing some disorders, as outlined in Table 1. Therefore, health policies and clinical practice models should prioritize vaginal childbirth and re-evaluate when C-section is medically necessary.[110] One further part of the puzzle is the recent postulation that the process of microbial gut colonization may be initiated prenatally by a distinct microbiota in the placenta and amniotic fluid.[111] However, the relative contribution of this to postnatal colonization in either C-section or vaginally born infants is unclear, especially as only the presence of bacterial DNA, not live microbes, has been shown in the placenta.

Probiotic supplementation

Probiotics are live microorganisms that, when administered in adequate amounts, confer health benefits on the host.[112] Probiotic administration confers a plethora of beneficial effects in a variety of disorders, such as inflammatory bowel disease, irritable bowel syndrome, obesity, diabetes, and asthma.[112] The mechanisms by which probiotics exert these positive effects on the host are the focus of a number of preclinical and clinical investigative studies. For example, one study demonstrated that consumption of the commensal bacteria *L. rhamnosus* GG by the mother affects fecal *Bifidobacterium* transfer and composition during early infancy.[113] In other words, supplementation with this bacteria appears to reinforce the development of a more complex and diverse *Bifidobacterium* microbiota.[113] A separate study determined that treating expectant mothers with *L. rhamnosus* GG confers this strain to the newborn infant, with its presence documented for at least 6 months and, only in certain cases, persisting for as long as 24 months.[114] In addition, infants whose mothers received *L. rhamnosus* GG during late pregnancy are more often colonized with species belonging to the most abundant group of *Bifidobacterium* microbiota present in the intestine of healthy infants and in human breast milk, *B. longum,* than infants whose mothers received placebo.[114] However, it is worth noting that a separate clinical study reported that *L. rhamnosus* GG fails to modulate the microbial diversity of early infant gut microbiota despite promoting a beneficial *Bifidobacterium* profile.[115] These results suggest that administration of potential probiotics to expectant mothers during late pregnancy can have beneficial effects on the development of the infant's intestinal microbiota. Thus, probiotic treatment during pregnancy may represent an effective strategy to promote a healthy microbial composition in babies born via C-section. Moreover, systematic reviews of different studies suggest that the administration of certain

probiotics to premature infants reduces the incidence of necrotizing enterocolitis, with resultant significant improvements in survival rates.[116,117] To date, prophylactic administration of probiotics to premature infants (<32 weeks gestation) may be the only clinical circumstances in medicine where probiotic administration has been shown to save lives.

Prebiotic supplementation

In addition to probiotics, prebiotics have demonstrated promising effects in ameliorating immune and microbiota-derived health impairments.[118] Prebiotics are "non-digestible substances that provide a beneficial physiological effect for the host by selectively stimulating the favorable growth or activity of a limited number of indigenous bacteria."[111,119–123] It is important to note that although all prebiotics are classified as dietary fiber, not all fiber is prebiotic: to be a prebiotic, the ingredient must not be digested in the upper gastrointestinal tract, must be fermented by the gut microbiota, and must stimulate the growth/activity or beneficial microbes, usually lactobaccilli and bifidobacteria.[124] When prebiotics are fermented by these bacteria, short-chain fatty acids, lactic acids, and acetic acids are produced, which can have profound effects on host metabolism.[122] Prebiotics occur naturally in foods such as vegetables, wheat, and soybeans and are typically oligosaccharides or more complex saccharides. So far, the most commonly studied compounds include inulin, fructo-oligosaccharides, and galacto-oligosaccharides.[122,124]

Preclinical studies using mice suggest that maternal consumption of fructo-oligosaccharide diminishes the severity of atopic dermatitis-like skin lesions in the offspring,[125] suggesting that these compounds have a positive effect on the immune system. Another study in mice suggests that altering the fiber content of the maternal diet during both pregnancy and lactation enhances offspring growth through an effect on intestinal and muscle mass rather than fat mass accretion.[126] In addition, results in piglets demonstrate that supplementation of prebiotics (short-chain fructo-oligosaccharides and polydextrose) modulates microbial colonization and alters signaling of short-chain fatty acids.[127] Clinical studies have also reported that early prebiotic supplementation (such as with galacto-oligosaccharide and polydextrose) during the first 2 months of life may alleviate symptoms associated with crying and fussing in preterm infants.[128] Moreover, prebiotic supplementation in the early neonatal period increases the prevalence of *Bifidobacterium longum* in the infant gut, in addition to promoting strain diversity.[129] Although limited so far, these data suggest that prebiotic supplementation in infants exposed to early-life microbial perturbation may represent a viable strategy to benefit not only the gut microbiota, but also immunity,[130–132] metabolism, and gastrointestinal function.[122,124]

Synbiotic supplementation

The combination of pre- and probiotics is thought to have synergistic beneficial effects on the immune and metabolic systems. Modification of the gut microbiota with a combination of specific prebiotics and probiotics (knows as synbiotics) might offer a novel and cost-effective strategy to reduce the risk of rhinovirus infections[133] and to restore the delayed colonization of *Bifidobacterium* spp. in C-section-delivered babies.[134] Indeed, evidence from clinical[135] and preclinical[136] studies indicates that some allergies can be prevented by using synbiotics. Synbiotics may increase the total antioxidant capacity levels in breast milk.[137] Moreover, synbiotics may prevent weight loss in lactating mothers and increase the weight gain of infants.[138]

Human milk feeding

Natural selection has influenced the coevolution of hosts and microbes. This is clearly evidenced by mammalian mother-infant dyads, as the human microbiota is shaped by mothers and breast milk.[139,140] Microbes are present in breast milk and may contribute to the composition of the infant microbiota,[140,141] although this is, at present, an open question. Human breast milk consists of over 200 prebiotic oligosaccharide isomers, which influence the colonization and maturation of the infant gut microbiota.[139] Oligosaccharides typically pass undigested from the infant stomach and are the major carbon source available to gut bacteria.[142] Indeed, variation of the oligosaccharide profile in milk influences the microbial establishment in the infant gut.[63] Importantly, the preponderance of the "breastfed-infant-type" of bacteria, ie, *Bifidobacterium* species, *B. longum* subsp. *infantis* – a species capable of utilizing the major oligosaccharides in human milk[143] – is associated with better infant health and development.[144,145] Therefore, the combination of probiotic and prebiotic components of human milk provides human milk–fed infants with a stable and uniform gut microbiota.[146]

It is consequently not surprising that the infant feeding regimen, ie, whether the infant is fed with formula or human milk, impacts the developing gut microbiota. Recent extended analysis of the Human Microbiome Project showed that it was possible to detect a microbial signature indicating whether an individual was ever or never breastfed as an infant.[147] Evidence suggests that bacteria stimulated by human milk feeding can activate more immunoprotective genes

in the host compared with formula feeding,[148] and an extensive literature review has linked human breastfeeding with optimal infant health.[149] Rhesus macaque infants that are breastfed by their mothers have a distinct microbiota profile and an expansion of Th17-based immune response in comparison with bottle-fed counterparts. In particular, human milk–fed infants develop robust populations of memory T cells as well as T helper 17 cells within the memory pool, whereas bottle-fed infants do not.[150] In contrast, formula-fed infants have more diverse gut microbial communities typified by higher populations of *Clostridium, Franulicatella, Citrobacter, Enterobacter*, and *Bilophila* species compared with human milk–fed infants. Functionally, these formula-fed infants hosted higher proportions of antibiotic resistance genes, especially from ɤ-Proteobacteria.[151] This suggests there may be previously unconsidered benefits from human milk, including that it reduces exposure to populations of microbes that contribute to antibiotic resistance.[151] Given the numerous documented health advantages of breastfeeding and human milk, feeding infants human milk when possible represents a potential strategy to counteract early-life microbial perturbations including C-section delivery. However, it is important to acknowledge that since C-section delivery can impede early breastfeeding,[15] this may not be a viable option in all cases.

Infant formula feeding with specific fatty acid supplementation

Human breast milk contains critical polyunsaturated fatty acids. Thus, another potential intervention strategy could be supplementation of infant milk formula with long-chain fatty acids such as docosahexaenoic and eicosapentaenoic acids and other n-3 polyunsaturated fatty acids, which have been extensively described in studies on allergic diseases, asthma, inflammatory bowel disease, and early-life stress.[153–155] In fact, in clinical studies, n-3 polyunsaturated fatty acid consumption during pregnancy and infancy have been shown to prevent and/or improve onset and development of asthma;[156] however, more research is warranted to determine the mechanism and the impact of dietary fatty acids on the intestinal microbiota composition of the host. It is possible that dietary supplementation with n-3 long-chain polyunsaturated fatty acids may exert indirect benefits in pregnancy through inhibition of placental inflammation.[157] More specifically, some studies show the influence of dietary-specific docosahexaenoic acid and arachidonic acid on infant CNS with implications for neural development.[158] It has recently been shown that a combination of docosahexaenoic acid and eicosapentaenoic acid could reverse the impact of early-life stress on the microbiota.[155]

Promoting breastfeeding and the use of human donor milk and breast milk fortifiers

Promoting exclusive breastfeeding for at least 6 months is the best approach to ensure the generation of a healthy microbiome in the infant. Mothers of preterm infants often cannot breastfeed. In these cases, human milk from human milk banks may be a possible alternative to improve neonatal health. However, strategies to boost donation rates should be identified to maintain donor human milk availability for preterm infant nutrition.[159] Moreover, barriers remain for such availability including in terms of safety (eg, health status of mother, milk quality[160]) and variability in expressed milk composition (foremilk vs hind milk can vary in fatty acid composition),[161] and the metabolome of preterm milk changes within 5 to 7 weeks postpartum to resemble that of term milk (eg, glutamate, caprylate, and caprate levels are increased in mature-term milk compared with colostrum).[162] Logistical barriers such as monetary donations and shipping the milk over long distances also likely influence the availability of donor milk.[163] Moreover, the impact of pasteurization on donor milk quality and the bioactivity of milk proteins/peptides should be minimized. All of these aspects indicate there should be more promotion and financial support of intrahospital human milk bank units to support the safe use of human milk in preterm infants. In the early weeks of their lives, premature infants are often fed maternally expressed breast milk enhanced with bovine-derived fortifiers to improve caloric intake and provide minerals, especially calcium and phosphate, to enhance bone health, and to prevent neonatal rickets. Human milk–derived fortifiers are currently being used in some neonatal centers as an alternative to bovine-derived fortifiers, albeit an expensive one. Whether using human fortifiers offers clinically measurable benefits and/or a more favorable microbiome composition compared with bovine-derived fortifiers remains to be seen.

Perspectives for the future

Thirty years ago, when experts from the World Health Organization met in Brazil to address the various issues surrounding childbirth, they agreed that there was "no justification for the rate of C-section exceeding 10-15% in any region of the world." That percentage was then turned into a kind of universal dogma, valid for any hospital, anywhere in the world. However, while the C-section rates have continued to increase, the evidence collected in the past 3 decades has shown that this standard figure is not well adjusted to the complex and changing environment of labor. The World Health Organization itself revised its statement on the ideal

Table 2 **Summary of different strategies involved in restoration of the gut microbiota after C-section**

Strategy	Featured effects	References
"Vaginal seeding"	Vaginal seeding could successfully colonize C-section infants with vaginal bacteria	Dominguez-Bello et al. (2016),[101] Knight et al. (2016)[105]
Microbial environment	Green spaces/natural environments rapidly induce positive changes to the psychological, physiological, and endocrine systems; diminished exposure to them in the perinatal period may cause immunoregulatory and psychosocial deficits	Rook (2013)[109]
Probiotic supplementation	Supplementation with probiotics can confer a plethora of beneficial effects in variety of disorders, eg, consumption of the commensal bacteria *L. rhamnosus* GG affects fecal *Bifidobacterium* transfer and composition during early infancy	Hill et al. (2014),[112] Gueimonde et al. (2006)[113]
Prebiotic supplementation	Supplementation with prebiotics may represent a viable strategy to benefit the gut microbiota, immunity, metabolism, and gastrointestinal function of infants exposed to early-life microbial perturbation	Rastall et al. (2015),[123] Slavin (2013),[124] Barrett et al. (2015),[129] Arslanoglu et al. (2008),[130] Gruber et al. (2010)[131]
Synbiotic supplementation	Supplementation with a combination of pre- and probiotics can have synergistic beneficial effects on the immune and metabolic system	Passeron et al. (2006),[136] Nikniaz et al. (2013),[137] Ostadrahimi et al. (2013)[138]
Human milk feeding	Microbial establishment in the infant gut is influenced by the microbes present in breast milk	Diaz Heijtz (2016),[64] Hinde et al. (2012)[139]
Specific infant formula feeding	Supplementation of infant milk formula with long-chain fatty acids may prevent and/or improve development of asthma, inhibit placental inflammation, and have implications for neural development - even potentially reversing the impact of early-life stress on the microbiota	Miles et al. (2014),[156] Melody et al. (2015),[157] Hsieh et al. (2009),[158] Pusceddu et al. (2015)[155]
Human donor milk banks	Can be used as a possible alternative to maternal breastfeeding to improve neonatal health by supporting the safe use of human milk in preterm infants	Stevens et al. (2015),[159] MacKenzie et al. (2013)[163]

C-section rate in April 2015, adding that "rates above 10% are not associated with a reduction in maternal and neonatal mortality." The following phrase was also added, which was not in the 1985 document: "Every effort should be made to perform C-sections to all women who need it rather than trying to achieve a certain rate."[164]

Like any surgery, C-section is not without risk. C-section surgery increases the risk of bleeding (and subsequent anemia), uterine ruptures, and problems with the placenta that can penetrate the wall of the uterus or complicate future pregnancies.[165] Thus, the enduring risks associated with C-section delivery are now also beginning to be uncovered, and it is becoming clear that they are not limited to the mother. For example, compared with children born vaginally, children entering the world via C-section have an increased risk of asthma.[77,166] The sensitivity of the newborn's microbiome also should not be underestimated, as it can be affected by the location of birth, the type of birth, and the interventions, particularly maternal and infant antibiotic use, that may occur during or soon after birth. Most C-sections are accompanied by prophylactic maternal antibiotic administration that may affect the microbiota composition of the infant gut through subsequent breastfeeding.[167] Therefore, the impact of C-section delivery on infant and maternal health as well as the microbiome should continue to be investigated.

Improving infant and maternal health

It should also be noted that maternal transfer of microbes may not always be beneficial. Indeed, studies in animals and humans show that maternal stress changes both the vaginal and offspring microbiota.[168,169] Similarly, maternal pregestational weight correlates with offspring birth weight, and maternal obesity has been linked to fetal overgrowth, congenital defects, neural tube defects, stillbirth, preterm delivery, child morbidity, respiratory problems such as asthma, and neonatal mortality.[170–172] The maternal gestational environment may create long-lasting and/or permanent modifications in fetal physiology, which can increase the risk of developing obesity, diabetes, and cardiovascular diseases in adulthood.[173] Therefore, C-section with normative microbial interventions is a promising strategy warranting further investigation. Finally, health promotion strategies to lower the C-section rates and to

educate against the potential risks are important strategies for the future, especially in jurisdictions where there are very high rates of C-sections.[174]

CONCLUSION

While research into the role of the gut microbiota on infant development and health is ongoing, a better understanding of the relevant communities of bacteria in the gut of healthy and compromised infants is needed. The relative contributions of biodiversity, mode of delivery, the introduction of pre- or probiotics in infant nutrition, feeding regime, and nutritional supplementation determine the diversity, abundance, and ratio of the gut microbiota. This bacterial community then becomes the fundamental core of commensal gut bacteria for one's lifespan. As such, it is critical to unravel/decipher the links between gut microbiota composition and neurodevelopmental disorders and expand this important field of research. There is an excitement in the field about "seeding approaches" to reverse the effects of C-section delivery mode on the microbiome in early life, but there is an equal level of concern about the widespread utility and safety of this approach.[102,105] Thus, targeted nutritional or environmental interventions and readjustments in obstetrical and newborn medicine practices may be the best strategies to compensate for early-life microbiota disturbances in the future (Table 2). Furthermore, there is a need to perform more in-depth studies on the role of the microbiota in neuropsychiatric disorders, such as autism, schizophrenia, and depression,[14,175] in relation to mode of delivery and the possible consequences of this in later life. Future studies could also focus on the role of the microbiota in mediating fundamental brain processes ranging from prefrontal cortex myelination[176] to amygdala function[177] and hippocampal neurogenesis.[62] Moreover, the potential of psychobiotics[178,179] as novel nutritional strategies for brain disorders warrants further attention. Finally, the interventions and potential strategies detailed in this review are focused on microbiota-induced influences on the brain, but many will equally have implications for the impact of the microbiota on all systems in the body[180] and, thus, should not be examined in isolation in future analyses.

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