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Microbiota and Neurodevelopmental Trajectories – Role of Maternal & Early-life Nutrition

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Abstract

Pregnancy and early life are characterized by marked changes in body microbial composition. Intriguingly, these changes take place simultaneously with neurodevelopmental plasticity, suggesting a complex dialogue between the microbes that inhabit the gastrointestinal tract and the brain. The purpose of this chapter is to describe the natural trajectory of microbiota during pregnancy and early life, as well as review the literature available on its interaction with neurodevelopment. Several lines of evidence show that the gut microbiota interacts with diet, drugs and stress both prenatally and postnatally. Clinical and preclinical studies are illuminating how these disruptions result in different developmental outcomes. Understanding the role of the microbiota in neurodevelopment may lead to novel approaches to the study of the pathophysiology and treatment of neuropsychiatric disorders.

Introduction

The connection between the brain and the gastrointestinal tract has been extensively studied, but the existence of a bidirectional microbiota-gut-brain axis has only received attention in the last decade [1, 2]. The individual microorganisms that live in our body, the microbiota, and their collective genomes, the microbiome, exert considerable influence over host brain and behaviour [3, 4]. (Table 1). Variations in microbiota composition have been linked to neuropsychiatric disorders, including autism, stress, anxiety and major depressive disorder [3, 5].

Almost 30 years ago, it was proposed that prenatal and postnatal environmental factors interact with genetics to program health and disease in adulthood [6, 7]. Building on Barker's hypothesis, it was recently proposed that the microbiota could play an important role in programming adult brain health and disease [8]. Whether diet or other factors, such as stress and drugs, interact with the microbiota in early life to program brain health is currently being addressed by clinical and preclinical studies. This chapter reviews the natural trajectory of the composition of the microbiota during pregnancy and early life and outlines the current knowledge on the interaction between the microbiota and neurodevelopment.

Early-Life Neurodevelopmental Plasticity and the Microbiota

Dramatic structural and functional changes in the brain are characteristic of the first years of life. This neurodevelopmental plasticity requires timely and adequate migration, division and differentiation of neuronal and glial precursors [9]. Neuronal migration and axonal guidance establish short- and long-range connections that enable the recruitment of multiple brain areas for the execution of complex behaviours [10, 11]. Differentiated oligodendrocytes insulate neuronal axons with a myelin sheath to guarantee proper conductance of neuronal signals [12]. A growing emphasis is now placed on the role of astrocytes and microglia in facilitating synaptic pruning during early life through adolescence, allowing later in life the fine tuning of complex

circuits [13]. Plasticity is a key feature of the standard neurodevelopmental trajectory and modulates the dynamics of synaptic connections and neural circuitry formation. Deviations from the neurodevelopmental trajectory can account for increased susceptibility to brain diseases later in life.

There is a growing appreciation of the link between neurodevelopment and intestinal microbiota. Studies in germ-free mice have shown abnormal brain development, especially in male mice [14–16]. More recent studies in these microbiota-deficient mice have shown altered expression of genes implicated in neurophysiology processes, such as neurotransmission, neuronal plasticity, metabolism and morphology in the amygdala [17] and hippocampus [18]. Hypermyelination in the prefrontal cortex and abnormal microglia maturation characterize the glia profile of these animals [19–23]. Furthermore, they showed increased blood-brain barrier permeability [24]. Functionally, such changes translate to increased stress response [14, 16], changes in anxiety [25] and fear recall [26], cognitive deficits [27], social changes [21, 28] and visceral pain responses [29]. Thus, the complete absence of microbial colonization in early life has dramatic effects on offspring's brain development and function (Table 1).

Dynamics of the Maternal Microbiota during Pregnancy

Pregnancy is a unique period in human life, and both the gut and vaginal microbiome have evolved to follow an optimum trajectory to support the mother and the developing fetus and allow for the ideal handover of microbiome at birth, informing maternal and child health outcomes.

The human female gut microbiota undergoes dynamic compositional changes across gestation [30–32]. As pregnancy progresses, a reduction in the diversity of the intestinal microbiota takes place, characterized by an enrichment in Proteobacteria [30]. This natural shift in the bacterial populations is functional to the increased metabolic demands by the developing fetus. The Proteobacteria expansion can help the body with the increased energetic

requirement that is characteristic of the third trimester [33]. Interestingly, when gut microbiota from this time period was transferred to microbiota-depleted rats, they showed increased adiposity, reduced glucose tolerance and inflammation, signs of metabolic syndrome [30]. This suggests that the changes in gut microbiota composition during pregnancy have an adaptive role for maternal and newborn health.

The vaginal microbiota composition also changes during pregnancy towards a less diverse configuration [34, 35]. As with gastrointestinal microbiota, the change in vaginal microbiota has a specific role during pregnancy. An increase in the presence of *Lactobacilli* helps maintain a low pH, limiting bacterial growth opportunity for other bacteria [35]. Furthermore, vaginal microbiota composition is critical in the context of vertical transmission of microbial populations [36]. Whether interventions in the physiological trajectory of maternal microbiota could alter the prenatal environment and, in turn, deviate normal brain development is a key question in neuroscience that is starting to be addressed both in preclinical and clinical areas (Fig. 1).

Preclinical Models of Early-Life Microbiota Trajectory

Similar to humans, mice and rat intestinal and vaginal microbiota go through compositional changes during pregnancy, providing a robust preclinical model for studying the link between maternal gut environment and offspring brain development [37–40]. Early gestation is characterized by a transitional increase in the relative abundance of *Akkermansia* and *Bifidobacterium*, which in late pregnancy decrease to levels seen in non-pregnant mice. In contrast, *Bacteroides* remain relatively elevated throughout pregnancy [37]. Interestingly, microbiota compositional changes also occur post-partum. The relative abundance of Actinobacteria increases early post-partum, while the one of Bacteroidetes decreases [38].

The vaginal microbiota has its own trajectory in pregnant mice. After the first week of pregnancy, there is an increase in bacterial diversity characterized by a growth of the Firmicutes

and Bacteroidetes phyla [40, 41]. The changes seen in mice gut microbiota during pregnancy and post-partum make it a solid approach to the study of interventions in the maternal microbiota and the impact on offspring's neurodevelopment.

External Challenges to Maternal Microbiota Dynamics

Given the importance of early-life microbiota in neurodevelopment, any factor that affects its composition has the potential to influence brain health. Indeed, a variety of exogenous factors affect the trajectory of microbiota composition during pregnancy. Diet, drugs, infection, hospitalization, prematurity and stress are among the influences that divert maternal microbiota from its natural course and impact on offspring's brain, immune system and the hypothalamic-pituitary-adrenal axis (HPA) development.

Diet and Maternal Microbiota

Diet is one of the major sculptors of the diversity and abundance of the intestinal microbiota [42]. Inadequate intake of macronutrients or micronutrients during pregnancy has been related to altered maternal microbiota [43] and offspring's poor neurocognitive outcome (Table 2) [44]. This association suggests a role for the maternal microbiota in brain prenatal programming.

One of the most common macronutrient consumption imbalances during pregnancy is the consumption of high-fat diets. Maternal overweight has been associated in humans with increased risk of poor neurodevelopmental outcomes [45]. In rodents, consumption of a high-fat or Western diet prior and during pregnancy impairs the trajectory of maternal and offspring's microbiota [37, 46]. This alteration was associated with a neuroinflammatory profile in the hippocampus and amygdala of the offspring, resulting in juvenile impaired social behaviour and anxiety-like phenotype [47]. Interestingly, a high-fat diet prior to and during pregnancy impairs maternal HPA axis plasticity and the offspring's hypothalamic gene response to stress [48, 49]. However, caution is required when interpreting the literature on the neurobiological changes

induced by diets rich in fat and sugar in rodents as the content of the control diets regarding fibre and other nutrients needs to be taken into account [50, 51]. Nevertheless, preclinical studies on maternal high-fat and Western diets (see [8] for an extensive review) support the idea of a role for diet-induced microbiota changes in brain programming.

During fetal development, micronutrients are required for neurological development. Deficiency in B vitamins, folate or ions, such as iron and zinc, exerts detrimental effects on neurocognitive development in humans and rodents [52, 53]. Folate deficiency is paradigmatic of the impact of micronutrient deficit on offspring neurodevelopment. Mammalian cells are unable to synthetize this vitamin; thus, humans depend on food or supplements to compensate for their requirement [54]. Failure to achieve normal serum folate levels during pregnancy has been associated with increased neural tube defects in the offspring [55]. Conveniently, bacteria residing in our colon can produce many vitamins of the B group, including folate. In mice, a loss-of-function mutation in an intestinal folate transporter can account for folate malabsorption, suggesting that bacterial produced folate plays a major role in host metabolism [56]. In humans, consumption of a vegetarian diet during early pregnancy was associated with a distinctive microbial composition rich in biosynthesis pathways for fatty acids, lipids and folate [57].

Prebiotics and Probiotics

Research on the effect of prebiotic and probiotic administration during pregnancy is at an early stage (Table 3). Current reports indicate that the administration of prebiotics or probiotics to pregnant women is not associated with an increase or decrease in the risk of preterm birth or other infant and maternal adverse pregnancy outcomes [58]. Researchers are beginning to shed light on their effects on offspring's brain and immune development [58].

Prebiotics promote the growth of beneficial bacteria and include indigestible fibres that are fermented by colonic bacteria to produce short-chain fatty acids and provide a health benefit [59]. In humans, the effects of maternal intake of prebiotics on neurodevelopment have not been well studied, and there is uncertainty about their effects on allergy risk [60, 61]. Galacto-

oligosaccharide (GOS) and inulin administration to pregnant mice modulated the gut microbiota and prevented immune activation and intestinal permeability in the offspring [62]. Moreover, it has recently been shown that the addition of inulin to a mouse maternal high-fat diet abrogated the negative metabolic effect of the high-fat diet on offspring [63].

Probiotics are beneficial strains of bacteria that confer a health benefit to the host [64]. There is lack of research on the prenatal impact of probiotics on neurodevelopment in humans and rodents. Administration of probiotics to pregnant women impact on immunity, reducing the risk of atopy but not of asthma [65, 66]. More preclinical and clinical research must be conducted to determine the impact of prenatal probiotics on the maternal and offspring microbiota.

Drugs

Antibiotics

Antibiotics are widely used during pregnancy, but little is known about their effects on the trajectory of the maternal microbiome [67]. Preclinical models are starting to shed light on the effect of antibiotic exposure on offspring neurodevelopment. Administration of antibiotics to pregnant rats caused impairments in social behaviour and pre-pulse inhibition of the offspring [68]. In mice, administration of non-absorbable antibiotics during pregnancy reduced the exploratory behaviour in the offspring [69]. These results warrant further research on the effect of microbiota.

Psychotropics

Recently, Maier et al. [70] showed that a large amount of non-antibiotic human-targeted drugs have antimicrobial properties. Among them, drugs that can be prescribed during pregnancy, such as proton pump inhibitors, were found to disturb the growth of commensal bacteria (Table 2). Interestingly, psychotropic medications also influence the composition of gut bacteria in rodents [70, 71]. Selective serotonin uptake inhibitors, tricyclic antidepressants and antipsychotics negatively impact bacterial growth [71–73]. Looking at the effects on postnatal

development, prenatal exposure to fluoxetine induces an anxiety-like phenotype in rats [74]. Also, in rodents, valproic acid administration during pregnancy disturbs the microbiome of the offspring and results in impairment of the social behaviour of the offspring [75, 76]. Owing to the prevalence of psychotropic administration during pregnancy, it is crucial to characterize the interaction between maternal health, microbiota and offspring neurodevelopment (Table 2).

Stress and the Maternal Microbiota

In humans, prenatal and postnatal maternal stress has been associated with young adult offspring behavioural and depressive symptoms [77] and aberrant infant intestinal microbiota development (Table 2) [78, 79]. In rodents, prenatal stress shifts maternal gut and vaginal bacterial community and induces long-lasting alterations in the gut microbiota composition of the offspring [40, 80]. Moreover, this alteration was shown to occur in a sex-specific manner, and it correlates with hyper-reactivity of the HPA axis [40].

The Microbiota in Transition: from Prenatal to Postnatal

When the first contact with the microbiota occurs remains controversial. The sterility of the uterus during pregnancy is one of the paradigms that research on the microbiome is revisiting. Bacteria have been found in the placenta [81, 82], amniotic fluid and meconium of humans [83, 84]. Moreover, the presence of specific bacteria in utero has been associated with pregnancy risks, including higher rates of preterm delivery [85]. Nevertheless, the reliability of these findings is widely debated in the context of whether it is contamination or not [86, 87]. The existence of germ-free mice models further dismisses the idea of a prenatal microbiome [86]. It is generally accepted that the moment of birth is the first opportunity for large-scale bacterial colonization of the newborn. Thus, the mode of delivery has a tremendous impact on the establishment of the microbiota of infants.

Early-Life Microbiota and Birth Mode

A large number of studies associate the mode of delivery to a distinctive trajectory of microbiota development in the newborn [35, 36, 66, 88–99]. Unexposed to the birth canal, Caesarean section (C-section)-born babies elude mother-neonate vertical vaginal transmission of bacteria and viruses [36, 89, 100]. In turn, the microbiota resembles skin and environment microbiota, suggesting that C-section first colonizers come from diverse sources (Table 2) [35, 89].

That said it is worth reinforcing that mode of delivery-induced changes in microbiota composition are transitory. Vaginally delivered infants have significantly higher microbiota richness and diversity than C-section-born infants as early as 3 days after birth [88, 100–102]. Nevertheless, the early decline in Proteobacteria and the late Firmicutes expansion occur timely over the first year of life of C-section-born infants [101].

The time course of these microbiota alterations overlaps with a critical period for neuro- and immune development (see [103] for extensive review). It has been suggested that C-section-distinctive microbiota composition plays a functional role in predisposing these infants to a greater relative risk of neonatal infections, allergy, asthma, obesity and type 1 diabetes [35, 101, 104–108]. Preclinical models of C-section suggest that the mode of delivery could impact on early neuronal maturation [109, 110]. Whether modifying the initial colonizing microbiota induces directly or indirectly different trajectories in brain development has yet to be deciphered.

Epidemiology studies have shown that C-section-induced changes in terms of brain health and school performance later in life are subtle at best [111, 112] and, in the case of autism, do not withstand correcting for familial confounding [111].

Various strategies have been designed to restore the normal trajectory of the microbiota [113]. Although controversial, artificial vaginal microbiota transference was performed to C-section-born infants to mimic vertical transmission [114]. Other interventions, including supplementation with probiotics and prebiotics, were proposed to decrease the impact of delivery mode on the microbiota.

Early Postnatal Perturbations of the Microbiota

Early postnatal life entails an intrinsic sensitivity to environmental factors. As with the maternal microbiome, infant exposure to differences in diet, drugs and stress can interfere with the trajectory of the microbiota and neurodevelopment in a manner that is characteristic of this developmental period.

Mode of Nutritional Provision in Early Life

The stability and composition of the early-life gut microbiota community is also dependent on diet [115]. Accumulating evidence suggests that breastfeeding and formula-based nutrition leave a distinctive fingerprint in the intestinal microbiota (Table 2). Gut bacterial composition of infants exclusively breastfed is characterized by higher relative abundance of *Bacteroides* and *Bifidobacterium* compared to the one from formula-fed infants [108, 116]. Furthermore, breastfeeding had a positive effect on myelination and increased general, verbal and non-verbal cognitive abilities during childhood [117]. The implications of these findings are still unclear, but longitudinal studies are starting to shed light on the effect of early-life nutrition on the temporal course of microbiota maturation.

Human breast milk has a unique composition that interacts with the developing gut microbiota. Culture-dependent and -independent techniques revealed that it is a source of bacteria [118]. Interestingly, the human milk microbiome can be influenced by maternal body mass index and mode of delivery [119]. The other main components of breast milk are human milk oligosaccharides, which act as prebiotics [120, 121]. Supplementation of infant formula with GOS increases the abundance of *Bifidobacteria* and *Lactobacilli* to levels reported in breastfed infants [122, 123]. Both breast milk microbes and prebiotics play a role in the standard gut microbial developmental trajectory.

Later in life, feeding transitions drive important changes in composition and functionality of the intestinal microbiota [36, 89, 124]. From breastfeeding to solid food, the microbiome transitions from being enriched in genes associated with digestion of sugars from breast milk,

vitamin production and iron transport to degradation of starch and high sugars [36]. Furthermore, the microbiota continues to undergo change; at 7–12 years of age, the composition and function of the microbiota remains significantly different from the one of adults [125], suggesting a role of the microbiome in the neurodevelopmental changes associated with adolescence.

Probiotics and Prebiotics

Most of the evidence available on the effect of early-life exposure to pre- and probiotics comes from preclinical studies. Early-life prebiotic administration in humans has shown effects on reducing the risk of atopy, an autoimmune disease [126], but neurodevelopmental outcomes have not been studied yet. In preclinical studies, oligosaccharides have been shown to modulate the gut-brain axis, highlighting the role of breastfeeding in neurodevelopment. Administration of the human milk oligosaccharides 3'Sialyllactose (3'SL) or 6'Sialyllactose (6'SL) to mice exposed to social disruption prevented stress-induced colonic microbial disruption and anxiety-like behavior [127]. Furthermore, fructo-oligosaccharide (FOS) and GOS administration attenuated corticosterone release in response to an acute stressor and protected the mice from the impact of chronic stress on the microbiota [128].

Preliminary clinical trials of probiotic interventions have yielded promising results with regard to reducing the risk for gastrointestinal problems, sepsis, allergies and even autism spectrum disorder and attention deficit hyperactivity disorder [129–134]. Several groups have now shown that early probiotic interventions mitigate the effects of early-life stress, maternal high-fat diet and maternal immune activation on infant outcomes [47, 135–138]. Oral administration at weaning of *Bifidobacterium fragilis* ameliorates the abnormal stereotyped and anxiety-like behaviours of the maternal immune activation mouse model of autism [136]. Probiotic administration during adolescence restores social interaction-induced long-term potentiation in an animal model of social impairment by maternal high-fat diet exposure [47]. In maternally separated rat pups, a combination of *Lactobacillus rhamnosus* and *Lactobacillus*

helveticus reduced pup corticosterone responses to stress and normalized fear behaviour [135, 137, 138]. Another probiotic, *Bifidobacterium infantis,* normalized behavioural deficits in adult rats exposed to maternal separation [139].

Although clinical evidence on the role of pre- and probiotics for neurodevelopment is still lacking, preclinical research gives cause for a focus on early-life microbiota interventions.

Drugs: Antibiotics and Beyond in a Paediatric Setting

Antibiotics are commonly prescribed during the first years of life, yet the effect on brain health programming is unknown. Longitudinal clinical studies support the idea that early-life exposure to antibiotics perturbs the natural trajectory of the microbial communities by altering their stability [140]. Furthermore, neonatal exposure to antibiotics in rodents not only altered the microbiota but also induced increased visceral sensitivity and long-lasting changes in brain cytokines and behaviour [141, 142].

The interaction between early-life exposure to psychotropics, neurodevelopment and the microbiota is currently unknown. Not only exposure to psychotropics mediated by breastfeeding but direct administration of these drugs early in life could impact the developing microbiota. Serotonin uptake inhibitors and atypical antipsychotics indicated for the treatment of paediatric psychiatric disorders are among the non-antibiotic drugs known to change the microbiome composition [70, 71]. Atypical antipsychotics indicated for the treatment of the irritability associated with autism spectrum disorders have been shown to inhibit gut bacteria [70]. At the same time, the composition of the microbiota of autistic patients was shown to be altered [143–147]. Whether there is an interaction between microbiota populations, psychotropic drugs and behaviour has yet to be determined.

Early-Life Stress

The impact of stress on the development of the HPA axis has been shown to contribute to the programming of brain health in later life [148]. Interestingly, evidence from preclinical studies shows that early-life stress also alters the microbiota. Maternal separation during early life

disrupted the microbiota of the offspring of rhesus monkeys and rats [149, 150]. Interestingly, a diet containing prebiotics in combination with live *Lactobacillus rhamnosus GG* attenuated the effects of early-life maternal separation on anxiety-like behaviour and hippocampal-dependent learning [151]. Germ-free mice were more vulnerable to restraint stress, resulting in higher adrenocorticotropic hormone and corticosterone in plasma [14, 16], a reduction in glucocorticoid receptor mRNA and an increased stress response [14]. Remarkably, these effects were rescued with microbiota transplantation during adolescence but not adulthood [14].

Future Perspectives

Pregnancy and the first years of life are unique stages of plasticity for the intestinal microbiota. In both cases, there is a dynamic trajectory of the intestinal microbiota composition that is functional to the requirements of the host. Although plasticity represents an opportunity for adaptation, it is also a vulnerable stage. As we have reviewed, clinical and preclinical studies suggest that diet, stress and drugs can interact with the natural trajectory of the microbiota and play a part in programming brain health (Fig. 1). However, the evidence is still scarce, and further research is needed to understand the functional implications of these interactions.

The nervous system and the microbiota show concurrent developmental trajectories, offering a unique opportunity for intervention. There is potential for the development of early-life-targeted interventions of the microbiome, aiming to reduce the risk of disease later in life. Further research is needed on the characterization of critical windows to modulate the microbiota and the consequences of early intervention.

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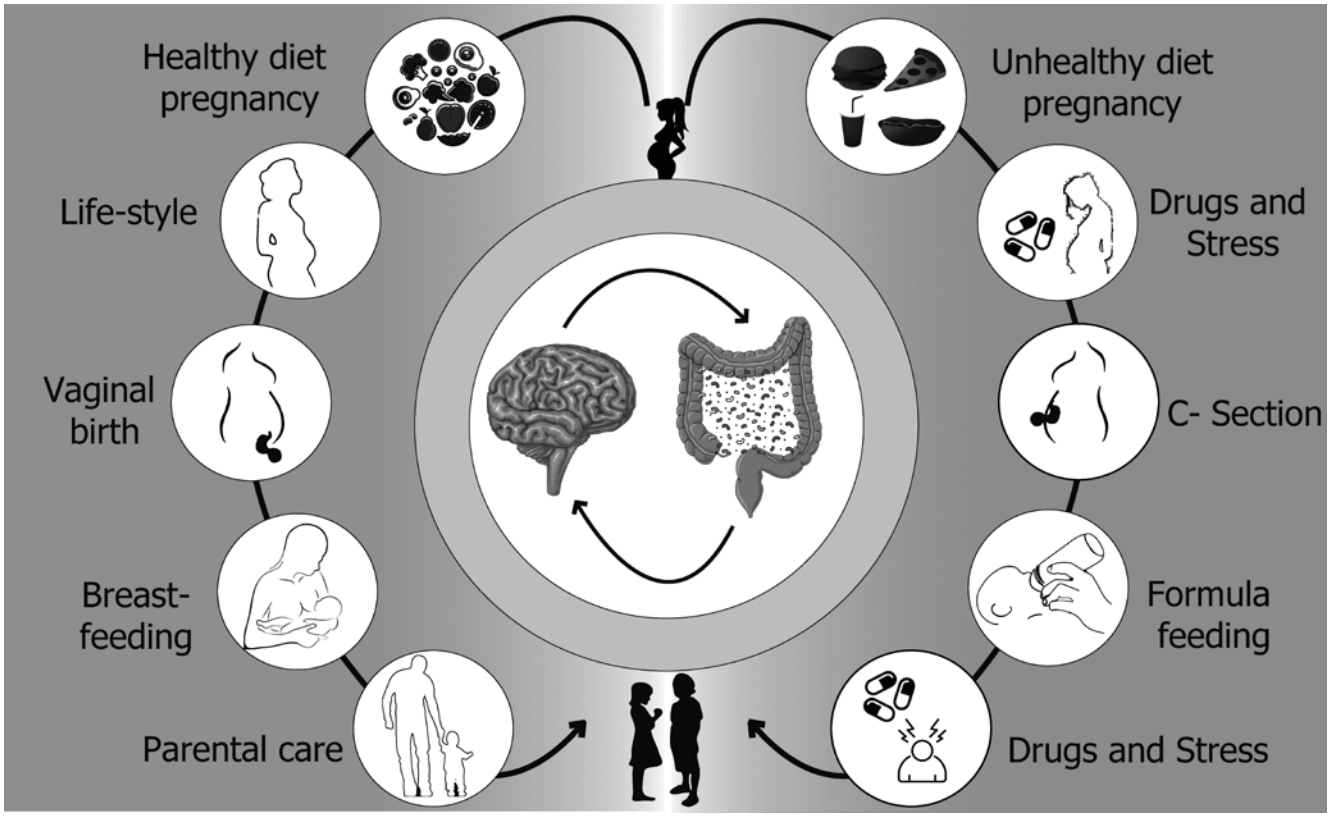
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Legend(s)

Fig. 1. Factors that determine the trajectory of the microbiota during early life. The gut and vaginal microbiome of the mother is altered by diet, drugs and stress. The mode of delivery determines the first colonizers of the newborn's gut. Early in life, diet, drugs and stress can also affect the infant microbiota composition.

Table(s)

Table 1. Glossary of terms related to the gut-brain axis

Term	Definition
Gut-brain axis	The multidirectional biological system comprising the central nervous system, the neuroendocrine and neuroimmune systems, the gastrointestinal tract and components of the enteric and autonomous nervous system
Microbiota	The collection of microbes (including bacteria, viruses and fungi) that inhabit a particular site
Microbiome	The totality of the microbial genes at a particular site
Host	The organism that houses a given microbial population

Commensal microorganisms	The intrinsic microbes that reside in the host
Prebiotic	Non-digestible foods that have a beneficial effect on the microbiome for the host
Probiotic	Live microbes that have a positive effect on host health when ingested in adequate quantities
Germ free	A host without a microbiome; generally refers to mice and rats that were born and reared in a sterile environment to keep them from developing a microbiome

Table 2. Factors that interfere with the gut microbiota trajectory during development

Factor		Effect on the microbiota	Ref.
Diet	pregnancy	Unhealthy diets can disrupt the natural trajectory of microbiota during pregnancy	[31]
	early life	Formula feeding is associated with a distinctive fingerprint in the intestinal microbiota ■■■	[108]
Mode of delivery	C-section is associated with a distinctive early microbial profile, dissimilar to the vaginal microbiota implicated in vertical transmission	[35]	
Drugs	non-antibiotic	Inhibition of commensal bacteria growth both during pregnancy and early life	[70, 140]
	antibiotic	Reduce the stability of early-life microbiota	
Stress	Prenatal and postnatal stress alter the composition of early-life microbiota	[78]	

Table 3. Interventions that support microbiota development

Factor	Effect on the microbiota	Ref.	

Diet	pregnancy	Diets high in fibre improve gut microbiota diversity	[152]
	early life	Due to its unique composition that includes prebiotics, breast milk supports early-life microbial development	[108]
Prebiotic	Growth stimulation of specific bacteria populations that is associated with a health benefit	[153]	
Probiotic	Modulates microbiota functionality, intestinal immunity and epithelial responsiveness In adequate amounts confers health benefits to the host	[154]	

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