

OPPORTUNITIES FOR THE APPLICATION OF THE GUT-BRAIN-AXIS MICROBIOTA FOR THE OPTIMIZATION OF NERVE GROWTH AND DEVELOPMENT IN INFANTS

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Abstract: Opportunities for The Application of The Gut-Brain-Axis Microbiota for The Optimization of Nerve Growth and Development in Infants. Neurodevelopment in infants is very important and has a significant role in shaping their future intellectual, emotional, and physical capacities. Nerve cells (neurons) form a neural network in babies from the time of pregnancy. The interaction between the gut microbiota and the brain occurs through a pathway called the gut-brain axis. Studies have shown that gut microbiota influences brain function and human behavior. To find out the efforts that can be made to maximize the development of the baby's brain by utilizing the concept of the gut-brain-axis microbiota. Using literature review techniques from international articles in the 2013-2023 using specific keywords in PubMed, Cochrane, Embase, Scopus, Google Scholar, and Textbook. Efforts to improve neurodevelopment using the concept of a gut-brain-axis microbiota are essentially efforts to create a good microbiota balance in the gut. These efforts include maintaining and maintaining the balance of the healthy microbiota of pregnant women, giving birth pre-vaginal, providing exclusive breast milk, reducing the use of antibiotics that are not required, providing complementary foods breast milk rich in probiotics and prebiotics, providing stimulus, and reduce the use of chemicals. The concept of gut-brain-axis microbiota is very applicable to maximize neurodevelopment in infants starting by paying particular attention to the prenatal and postnatal periods.

Keywords: Microbiota, gut-brain-axis, infant, brain development, nerve growth.

Abstrak: Peluang Penerapan Mikrobiota Sumbu Usus-Otak untuk Optimalisasi Pertumbuhan dan Perkembangan Saraf pada Bayi.

Perkembangan saraf pada bayi sangat penting dan memiliki peran yang signifikan dalam membentuk kapasitas intelektual, emosional, dan fisik mereka di masa depan. Sel-sel saraf (neuron) membentuk jaringan saraf pada bayi sejak dalam kandungan. Interaksi antara mikrobiota usus dan otak terjadi melalui jalur yang disebut poros usus-otak. Penelitian telah menunjukkan bahwa mikrobiota usus mempengaruhi fungsi otak dan perilaku manusia. Untuk itu, diperlukan pengetahuan tentang upaya yang dapat dilakukan untuk memaksimalkan perkembangan otak bayi dengan memanfaatkan konsep gut-brain-axis mikrobiota. Menggunakan teknik kajian literatur dari artikel-artikel internasional pada tahun 2013-2023 dengan menggunakan kata kunci tertentu di PubMed, Cochrane, Embase, Scopus, Google Scholar, dan Textbook. Upaya meningkatkan perkembangan saraf dengan menggunakan konsep mikrobiota usus-otak-poros pada dasarnya adalah upaya menciptakan keseimbangan mikrobiota yang baik di dalam usus. Upaya tersebut antara lain dengan menjaga dan mempertahankan keseimbangan mikrobiota sehat ibu hamil, melahirkan secara pervaginam, memberikan ASI eksklusif, mengurangi penggunaan antibiotik yang tidak diperlukan, memberikan makanan pendamping ASI yang kaya akan probiotik dan

prebiotik, memberikan stimulus, dan mengurangi penggunaan bahan kimia. Konsep gut-brain-axis microbiota sangat aplikatif untuk memaksimalkan perkembangan saraf pada bayi yang dimulai dengan memberikan perhatian khusus pada masa prenatal dan postnatal.

Kata kunci: Mikrobiota, poros usus-otak, bayi, perkembangan otak, pertumbuhan saraf.

INTRODUCTION

A baby's brain development in early years profoundly impacts later growth and development (Ackerman, 1992). During childhood, the brain can rapidly develop, forming the basis for intellectual, emotional, and social well-being (CDC, 2022). Genetic, environmental, dietary, and social factors influence brain development (Douet et al., 2014; Miguel et al., 2019; Georgieff et al., 2018; Grigorenko et al., 2017). To unlock a baby's potential, a supportive environment is essential, with a focus on nurturing a healthy gut microbiota through nutrition (Leeming et al., 2019).

The gut-brain axis facilitates communication between gut bacteria and the brain (Carabotti et al., 2015). The gut microbiota, housing bacteria, fungi, and viruses, plays a vital role in overall health (Jandhyala et al., 2015). Through various processes, such as hormone release and vagus nerve stimulation, this axis connects the gut and brain, influencing human behavior and brain function (Breit et al., 2018; Sudo, 2019).

Infants' gut flora profoundly impacts their health and development, with various factors like nursing practices, birth management, and lifestyle influencing it (Mueller et al., 2015). A healthy gut microbiota in infants supports their health and immune system balance (Mueller et al., 2015; Belkaid & Hand, 2014). Advances in knowledge and technology enable caregivers to promote baby brain development and establish a strong foundation, leveraging the gut-brain axis microbiota concept. This article explores initiatives to support newborns' brain development and overall growth.

DISCUSSION

Neurodevelopment in infants

Infants' neurodevelopment is pivotal for their future cognitive,

emotional, and physical abilities (Bush et al., 2020). The first three years are the prime period for neurodevelopment, marked by rapid brain growth and the establishment of vital neural connections (Committee on the Science of Children Birth to Age 8, 2015). Positive social and environmental interactions during infancy profoundly impact neurodevelopment (Miguel et al., 2019), whereas stress, poor nutrition, and exposure to toxins can hinder long-term development (Bush et al., 2020) (Tran & Miyake, 2017). Parents and governments must ensure optimal environments to promote healthy neurodevelopment.

During pregnancy, newborns begin building their neural networks composed of neurons (Konkel, 2018). In the first few months of life, these neurons grow rapidly (Ackerman, 1992), forming synapses that enable learning and response to the environment (Ackerman, 1992). Social interactions, like contact and communication, positively influence neurodevelopment (Yoshida & Funato, 2021).

Infants go through various neurodevelopmental stages (Villar et al., 2019). For instance, they exhibit reflexes at around three months, showing cognitive development around six months when they grasp the concept of fixed objects and start pointing at things they want (Beltre & Mendez, 2022). Genetic factors also play a role, although environmental and experiential factors are crucial (Bush et al., 2020).

In summary, newborns' neurodevelopment is pivotal for their future abilities, shaped by social, environmental, and genetic factors. Supporting infant neurodevelopment is essential for their well-being.

Interaction between gut and brain

A key topic that receives a lot of attention in both research and medicine is the link between the gut and the

brain via the gut-brain axis microbiota (Appleton, 2018). The colony of bacteria, fungi, and viruses known as the gut microbiota inhabits the gut and is crucial to maintaining human health (Thursby, 2018).

The gut-brain axis is a route that mediates communication between the gut bacteria and the brain (Carabotti, 2015). Through a number of processes, including the creation and release of chemical compounds, such as hormones and neurotransmitters, and the stimulation of the vagus nerve, which transmits information from the colon to the brain (Carabotti, 2015) (Breit et al., 2018), this system enables communication between the gut and the brain.

The interactions between the gut and brain via the bone marrow-backbone-gut and microbiota-gut-brain pathways have a substantial influence on brain health and function (Breit et al., 2018). These interactions entail a variety of activities, including brain communication, the synthesis of chemical compounds, and immune system participation.

One of the important procedures is the bone marrow-back-gut pathway, which includes communication between the CNS and the CNS via the vagus nerve. The vagus nerve connects the brain to the digestive and gastrointestinal systems. Microorganisms in the stomach can affect both the operation of the vagus nerve and the message transfer to the brain via this pathway. These signals may have an effect on the brain's cognitive, behavioral, and emotional functions (Breit et al., 2018).

The gut microbiome affects human behavior and brain function, according to studies (Clapp et al., 2017). For instance, a healthy gut flora can support mental health and emotional stability. On the other hand, disturbances in the gut microbiota might result in mental health issues as sadness and anxiety (Clapp et al., 2017).

Additionally, the gut microbiota plays a critical role in the synthesis of neurotransmitters including serotonin and GABA, which are crucial for controlling mood and behavior (Chen et

al., 2017). Additionally, studies have demonstrated that the gut microbiota may affect how the body reacts to stress and restore normal brain function that has been impaired by stress (Sudo, 2019).

In general, the gut-brain axis is an important and fascinating research topic since it links the brain and the gut bacteria. The findings of this study can aid in the development of novel treatments for mental health issues as well as our understanding of how the gut bacteria might impact brain function.

Factors influence the development of an infant's gut microbiota

The formation of the intestinal microbiota in infants begins in the womb and lasts throughout development (Muller et al., 2015). Research shows that several significant factors influence the development of the baby's gut microbiota.

Firstly, the psychological condition of parents plays a role. Greater microbial diversity in the gut microbiome of newborns was linked to more severe prenatal stress symptoms at each of the three phases of pregnancy ($p = 0.025$). Infants that experienced maternal stress in utero had higher levels of several bacteria, including *Lactobacillus* and *Bifidobacterium*. Infants that had experienced less stress have different *Bacteroides* and *Enterobacteriaceae*. The results imply that prenatal exposure to mild to moderate stress may be linked to an early-life microbial ecology that is better suited to flourish in the demanding postnatal environment. Under stressful circumstances, the gut microbiota may adapt by upregulating some beneficial bacteria (like *Bifidobacterium*) and downregulating potential pathogens (like *Bacteroides*) through epigenetic mechanisms or the fetal gut-brain axis. More recent research has also highlighted that postpartum depression also affects the composition of the gut flora of mothers and infants. However, the risk of gastrointestinal issues in children may be increased by prenatal usage of serotonin/norepinephrine reuptake

inhibitor (SSRI) medications for depression. Pretreatment based on antibiotic and fluoxetine combination may change microbial profile (Doroftei et al., 2022) (Weiss & Hamidi, 2023).

Secondly, parents' diet choices can influence their baby's gut microbiota. Diets high in fat or ketogenic diets can affect brain volume, while a high-fiber diet can lead to cognitive improvements. Different dietary patterns can also influence the abundance of certain bacteria, like *Lactobacillus* and *Bacteroidales_S24-7*, and impact the production of short-chain fatty acids (SCFA). Additionally, vitamin and mineral deficits can increase gastrointestinal permeability, contributing to gut dysbiosis. These dietary factors can have implications for cognitive function, as observed through measures like the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III). Furthermore, the consumption of certain foods, in conjunction with maternal smoking, has been associated with specific bacterial abundances, such as *Enterobacter asburiae* (Doroftei et al., 2022).

Thirdly, the microbiota present during pregnancy can affect the baby's gut microbiota development. Babies conceived by mothers with healthy and diverse gut microbiota tend to have more beneficial gut microbiota after birth. The maternal microbiota can also impact immune responses and epigenetic regulation during brain development (Muhammad et al., 2022).

Fourthly, gestational age plays a role in gut microbiota development. Infants born prematurely often have altered gut microbiota, characterized by decreased levels of *Bifidobacterium*, increased levels of *Lactobacillus*, and changes in the levels of neurotransmitters like GABA and PHE. These alterations are associated with abnormal brain development and an increased risk of autism spectrum disorder (ASD) (Bresesti et al., 2022).

Additionally, the method of childbirth affects the baby's intestinal microbiota. Babies born through vaginal delivery tend to have a gut microbiota more similar to their mother's, with higher levels of bacteria like

Lactobacillus and *Bifidobacterium*. In contrast, newborns delivered via cesarean section (C-section) may have greater interleukin-1 (IL-1) and interleukin-10 (IL-10) production, which has been linked to increased *Streptococcus* colonization. The difference in microbiota composition is attributed to exposure to the mother's birth canal bacteria during vaginal delivery, while C-section delivery reduces this exposure. Increased IL-1 production in response to the inflammatory process following a C-section may influence *Streptococcus* colonization in infants (Doroftei et al., 2022) (Cabre et al., 2022).

Furthermore, breastfeeding plays a crucial role in shaping a healthy gut microbiota. Breast milk contains prebiotics and probiotics that promote a healthy gut microbiota and enhance the baby's immune system. Research suggests that partially hydrolyzed cow's milk protein baby formula with added *Lactocaseibacillus rhamnosus* GG (PHF-LGG) can influence probiotic composition. Additionally, early-life supplementation with milk fat globule membrane (MFGM) has positive effects on cognitive development, infection risk reduction, and gut microbiota regulation. MFGM can inhibit the growth of harmful bacteria while promoting the growth of beneficial bacteria like *Bifidobacterium* and *Lactobacillus*. Moreover, MFGM has neuroprotective properties and benefits newborns' neurodevelopment due to its components like sphingomyelin, gangliosides, and lactoferrin, which play significant roles in brain growth and function (Shulman et al., 2022) (Mohamed et al., 2022).

Environmental factors, including the use of antibiotics, dietary choices, and exposure to chemicals, also impact the development of a baby's gut microbiota. For instance, antibiotics can reduce the diversity of the gut microbiota and slow the growth of beneficial bacteria. Exposure to substances like triclosan (TCS), bisphenol A (BPA), nanoparticles of polyester, chlorpyrifos (CPF), and Polybrominated diphenyl ethers (PBDEs) can have neurotoxic effects during

paternal phases. Other compounds like DEHP and PFAS have been linked to human dysbiosis of the microbiota (Walker et al., 2017).

Moreover, congenital metabolic disorders and dietary patterns that inhibit the growth of short-chain fatty acid (SCFA)-producing bacteria can affect gut microbiota development. Diets that promote proteobacteria abundance, such as Western or GSD diets, can lead to increased systemic inflammation and cytokine levels (Profio et al., 2022).

Lastly, napping habits have been associated with gut microbiota diversity and maturity. Daytime sleep is linked to bacterial diversity, while irregular and fragmented nighttime sleep is associated with bacterial maturity and enterotype. These connections between the gut, brain, and sleep have implications for behavioral outcomes, as

sleep patterns and bacterial markers can predict them. Ensuring good sleep and a healthy gut microbiota in infancy may promote lifelong health, as many adult illnesses have their origins in childhood (Schoch et al., 2022).

In summary, multiple variables can influence the development of a baby's gut microbiota, underscoring the importance of ensuring its healthy formation. This is crucial for a robust immune system and for preventing illnesses and issues associated with unfavorable gut bacteria.

Efforts to improve toddler brain collapse by using the concept of gut-brain-axis microbiota

The efforts that can be made to maximize the development of the baby's brain are succinctly depicted in figure 1, which will further describe the explanation.

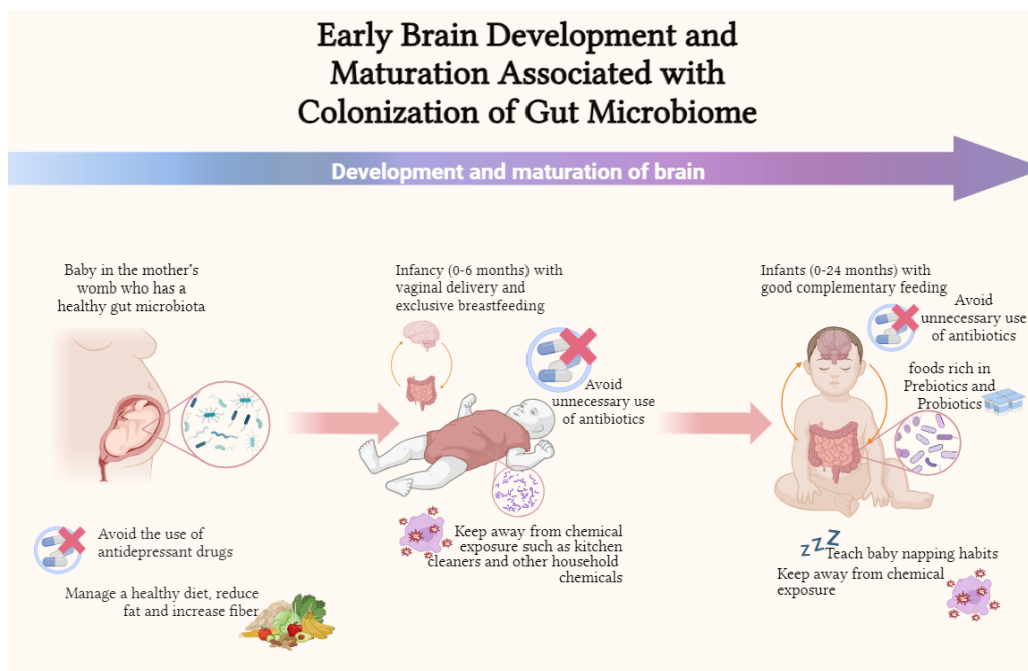


Figure 1. Improve brain development by using the concept of gut-brain-axis microbiota

The health of the gut microbiota is one element impacting neurodevelopment, which is important for the physical and mental development of infants. The collection of bacteria, fungus, and viruses known as the gut microbiota inhabits the gut and is crucial to maintaining human health.

A balanced gut flora has been linked to better neuronal function and mental stability in studies (Clapp et al., 2017). This is due to the production of neurotransmitters and hormones by the gut bacteria, both of which have an impact on nerve function (Chen & Chen, 2021).

To help prepare for a healthy baby gut microbiota, several things can be done, including:

1. Keep your mental wellness. The authors of this work advise parents to take care of their mental health even if prior research has revealed that stressful situations are linked to higher microbial diversity. Because in addition to these data, other investigations have shown that antidepressant medications that block serotonin reuptake can change the composition of the gut microbiota. The impact of stress on the fetus's overall neurological development requires further study.
2. Parents' diet. Keep a healthy diet for parents, not a lot of fat, high-fiber diet can help with cognitive improvements, don't get vitamin and mineral deficiencies, and don't smoke.
3. Prepare for labor well. Prepare your health so that the baby is not born prematurely, and prepare for vaginal delivery.
4. Giving exclusive breastfeeding for the first six months. Breast milk has the nutrients and antibodies a baby needs to build a healthy gut microbiota.
5. Avoid antibiotics unless necessary. Antibiotics can kill the good bacteria in the gut, which can disrupt the balance of the microbiota.
6. Provides foods rich in probiotics and prebiotics. Probiotics are good bacteria found in fermented products such as yogurt, kefir, and fermented milk, while prebiotics is foodstuffs that help maintain good bacteria in the gut.
7. Teach baby napping habits to create a healthy gut microbiome
8. Avoid using harmful chemicals. Keep away from environmental exposure especially chemical exposure containing triclosan (TCS), bisphenol A (BPA), polyester nanoparticles, chlorpyrifos (CPF), polybrominated diphenyl ethers (PBDE), DEHP, and PFAS. This chemical exposure such as kitchen cleaners and other household chemicals

To support your baby's healthy growth and gut microbiome, consult a

doctor for personalized advice. Maintaining a healthy gut microbiota is essential for proper neurodevelopment and overall well-being in infants. Factors like birth method, maternal diet, and parenting style can impact gut flora, so it's crucial to ensure its proper maintenance. Promote your baby's brain development through exclusive breastfeeding for six months, minimal antibiotic use, and a healthy diet. Probiotics and prebiotics can boost the immune system and foster a healthy gut flora.

Gut bacteria play a significant role in neurodevelopment by producing neurotransmitters like serotonin and dopamine. They also affect the immune and inflammatory systems, which impact brain health. Maintain a balanced gut flora with a balanced diet and regular exercise. Further research is needed to fully understand the connection between gut flora and neurodevelopment. Healthy gut flora acquired from the mother during nursing and delivery benefits neural development. Specific bacteria, such as Bifidobacterium and Lactobacillus, play roles in neurotransmitter synthesis and immunological activity. Fasting's impact on the gut microbiota is still being studied, so it's best to focus on a balanced diet, including fiber-rich foods, and avoiding processed foods. Complementary foods to breast milk influence the baby's gut flora balance, while prebiotic and probiotic-rich foods like fruits, vegetables, yogurt, kefir, kimchi, and tempeh can help maintain gut health.

Always seek medical or nutritionist guidance before introducing supplements to your baby's diet. Maintaining a strong microbiome balance is essential for their gut and overall health through a balanced, nutritious diet and judicious antibiotic use.

CONCLUSION

Efforts to maximize brain development in babies can basically start before the baby is born or in the prenatal mass. The first effort that can be made is to maintain a healthy balance of microbiota in the pregnant

mother's gut. Manage a healthy diet, reduce fat and increase fiber, and do not be deficient in vitamins and minerals. Next, maintain the health of the mother so that the child is not born prematurely. During childbirth, mothers should be advised to prioritize vaginal delivery because this helps the baby to get healthy microbiota from the mother which is useful for the baby's gut health. In addition, to maximize the growth of healthy gut microbiota and suppress the growth of unhealthy microbiota, it is recommended that babies aged 0-6 months be exclusively breastfed. After more than 6 months of age, babies are introduced to complementary foods until the age of 2 years. Complementary foods that are rich in prebiotics and probiotics are preferred. In addition, to maintain the health of the baby's gut microbiota so that it develops properly along with the baby's neurodevelopment, it is recommended to avoid using antibiotics if not needed, teach children to take naps, and avoid chemical exposure such as kitchen cleaners and other household chemicals.

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