ANATOMY OF THE DIGESTIVE SYSTEM IN NEWBORNS

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Annotation: This article comprehensively explores the unique anatomy of the digestive system in newborns, shedding light on the structural and functional aspects crucial for early development. From the esophagus to the large intestine, each component is dissected to provide a nuanced understanding of the digestive process in newborns. The developmental considerations and clinical insights offer , valuable information for parents, caregivers, and healthcare professionals, promoting awareness of normal variations and potential concerns in the newborn digestive system.

Key Words: Newborn Digestive System, Neonatal Digestive Anatomy, Esophagus in Newborns, Stomach Development, Small Intestine Function, Liver and Gallbladder in Neonates, Pancreatic Enzymes in Newborns, Large Intestine Maturation, Developmental Adaptations

Introduction. The maturation of the gastrointestinal (GI) system in full-term and preterm human infants is an area of great interest from both a nutritional and medical practice standpoint. Particularly in preterm infants less than 28 gestational weeks (GW), delivery constitutes a nutritional emergency in which the infant has high and difficult-to-meet nutritional needs . A contributing factor to the nutritional emergency is the relatively underdeveloped GI system of premature neonates, which limits their ability to utilize enteral nutrition. The GI system of preterm infants exhibits reduced digestive and absorption capacities, prolonged gastric emptying times, and limited intestinal motility compared to term infants. These same limiting factors that lead to a nutritional crisis alter the preterm infant's response to orally administered therapeutic agents.

The disorders of GI ontogenesis, along with other factors such as early postnatal stress, microbiota alterations induced by infections, or early antimicrobial use in the Neonatal Intensive Care Unit (NICU), result in an impaired activation of intestinal peristalsis and of the gut–brain axis. Disturbances of physiological inflammatory responses further contribute to this impairment. Abnormal development of bowel function is the main determinant of food intolerance, a major problem in the NICU.

Newborns need the structural and functional maturation of the GI tract for digestion and absorption of the nutrients from colostrum and breast milk. They also need a complete development of intestinal motor function which includes suck–swallow coordination, continence of the gastroesophageal sphincter tone, adequate gastric emptying, and intestinal peristalsis. Full-term babies can acquire adequate amounts of nutrients to promote the rapid growth that occurs shortly after birth. However, half of preterm infants are delayed in reaching full enteral feeding volumes and have gastroesophageal reflux, gastric residuals, and constipation due to delayed gastric emptying, prolonged bowel transit, abdominal distension, and delayed passage of meconium, all of which are GI functions describing immaturity . There are few studies available on fetal ontogenesis and early neonatal adaptation of motility and barrier functions of the human intestinal mucosa . The functional components of the human GI tract do not develop simultaneously: in fact, although the anatomical differentiation of the human intestine usually occurs within 20 GW, functional maturation is postponed over time and requires organized peristalsis and coordinated sucking and swallowing, which are not defined until 29–30 and 32–34 GW, respectively.

Understanding the functioning of the digestive system in children

Did you know that in order for a child's digestive process to take place completely, the child needs coordinated organs to perform each function separately, including: mouth, esophagus, stomach, intestines, liver, and pancreas.

Every time a mother breastfeeds, the oral cavity and tongue will act like a plunger to draw as much milk from the mother as possible. However, when the child is at this age, the oral mucosa of the child is quite soft, dry, has many blood vessels, so it is easily damaged and susceptible to fungal diseases in the mouth.

As your baby gets a little older and starts forming teeth, the teeth will help bite and crush food. Therefore, when your child starts teething, please give him solid and hard foods gradually.

After chewing the food thoroughly according to the instructions of the parents, the child will swallow the food through the esophagus to the stomach. After that, the food begins to continue the process of digestion in the stomach.

Your baby's stomach will have many changes during the child's development. At birth, a baby's stomach is round, lying high and horizontal. Therefore, the stomach muscles of children when they are young are weakly developed, especially the gastric sphincter, the stomach is easily deformed after eating while the pyloric sphincter is well developed and closes tightly, so the child is easy to vomit. after eating especially during the first 6 months of life.

After the stomach assumes and completes its function, the small intestine will receive the next substances of food. Parents see, the small intestine of the child is quite long, the intestinal mucosa has many wrinkles, microvilli and blood vessels, so it is easy for the child to absorb nutrients, but the connection between the intestinal epithelial cells is loose. Easy to create conditions for bacteria to enter causing digestive disorders. Moreover, the child's rectum is long, the muscles are weak and the mucosa is loose, so it is easy to prolapse when the child coughs and pushes a lot.

Next, food is digested in the intestine by the action of enzymes in intestinal juice, pancreatic juice, bile; However, the levels of these enzymes in children are lower than in adults, so children are prone to digestive disorders and malabsorption when they are ill.

Lactose is especially interesting from this perspective. Being the primary carbohydrate source in milk, lactose intolerance rarely occurs in the preterm population. Unabsorbed lactose conversion to SCFAs provides an efficient salvage pathway. One study suggests that lactase activity can be induced in preterm infants with enteral feedings of human milk.

Most lactase activity is found at the middle to the top of the villus, while sucrase, maltase and glucoamylase are found at the mid-villus. During time of intestinal mucosal injury, the lactase-rich cells at the villus tip are the first to be injured and the last to be fully restored through the process of cell migration from crypt to the villus tip.

Insulin plays an important role in intestinal maturation and may also contribute to improve lactase activity following preterm birth. Amniotic fluid contains carbohydrates, protein, fat, electrolytes, immunoglobulins, and growth factors. Insulin is present in the amniotic fluid (up to 20 μU/mL) and after skin keratinization completed (around 26 weeks' gestation), amniotic fluid is the main source of insulin exposure to the GI tract and plays a role in development. Preterm birth abruptly interrupts these important fetal life processes and the local insulin exposure of the GI tract with detrimental consequences.

Oral insulin administration in preterm infants up to 28 days after delivery has proved effective in doubling the lactase activity.

Lipids

Triglycerides constitute half of the non-protein energy content in human milk and formula. The digestion of triglycerides is initiated by bile acid micellar emulsification, which produces smaller droplets of triglycerides. This results in greater surface area for interaction with lipases, which hydrolyze long chain triglyceride into monoglycerides and free fatty acids, which in turn are absorbed into the small intestinal epithelium. Pancreatic lipase is one of the most important of these lipases.

The absorbed free fatty acids and 2-monoglycerides are re-esterified within the epithelial cell and subsequently converted to chylomicrons, which are transported from the basal region of the epithelial cell via the thoracic duct, from which they enter the blood circulation.

The digestion and absorption of medium chain triglycerides (MCTs) is less complex than that of long chain triglycerides. They do not require bile acid emulsification, are absorbed into the enterocyte without re-esterification and travel directly into the portal venous system. MCTs are frequently recommended for patients with lymphatic obstructions .

Different sources of lipase include lingual, gastric, pancreatic, and epithelial cells. Human milk contains a lipase termed bile-salt stimulated lipase. After activation in the small intestine in the presence of bile acids, it facilitates long-chain triglyceride digestion. Lingual lipase is secreted from glands at the base of the tongue; its activity is lower at birth in infants at 26 weeks' gestation, peaks at 30–32 weeks, and declines near term . Pancreatic lipase insufficiency is more prevalent in preterm infants when compared to older children. Adult levels are often not reached until 6 months after birth .

Another limitation of fat digestion relates to bile acids, which are synthesized and excreted from the liver via the biliary system at relatively low levels in very low birth weight (VLBW) preterm infants when compared to term infants. Bile ileal reabsorption is also lower in preterm infants, which results in less efficient lipid digestion when compared to term infants.

Essential fatty acids cannot be produced by the body and become deficient when not supplied in adequate quantities in the diet. To prevent deficiency, adequate dietary intake of linoleic and linolenic fatty acids can prevent deficiency. Furthermore, linoleic, and linolenic acids (18-carbons chain length) undergo desaturation and elongation enzymatic processes into long-chain polyunsaturated fatty acids (LCPUFAs) with more than 20-carbons. Required for formation of eicosanoids and central nervous system structures, it is concerning that preterm infants may not have the enzymatic capability to undergo these conversions. Many very preterm infants are provided formula that are not supplemented with these LCPUFAs, and even those receiving human milk may not receive adequate quantities of these important lipids.

Taking care of the digestive system in children

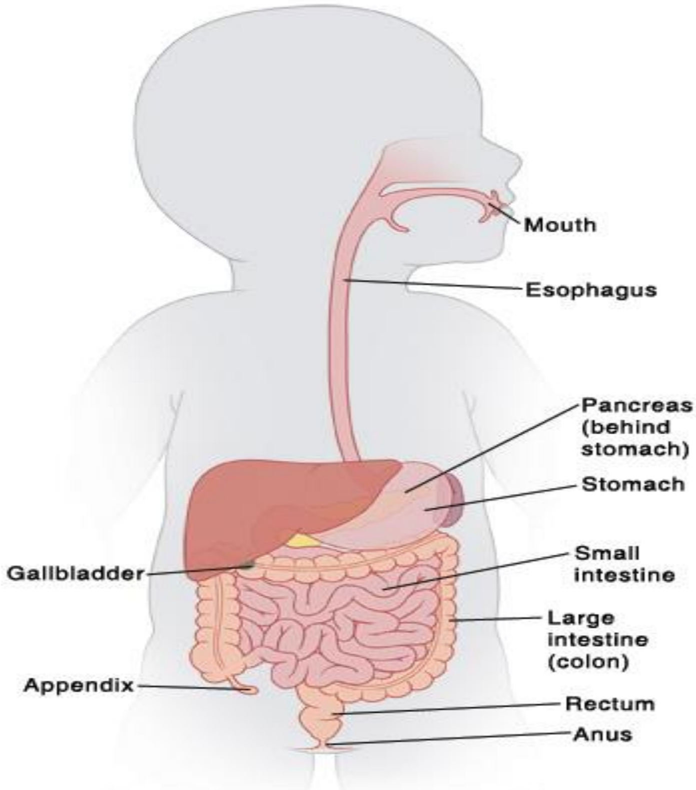
During the period of breastfeeding and mothers taking good care of hygiene, bacteria Bifidus, B.lactis aerogenes, B.acidophilus predominate because breast milk contains the sugar b lactose, which has a good effect on bifidus bacilli and inhibits bacteria. E. coli bacteria. If the mother breastfeeds her baby with formula milk, E. coli bacteria develop more because cow's milk contains a type of sugar called a lactose suitable for E. coli bacteria to grow. The positive effect of probiotics is to form a barrier to prevent pathogenic bacteria from entering, increase the digestion of proteins, fats, and sugars, participate in the synthesis of group B vitamins, vitamin K.

Another part of the baby's digestive process is the liver. The liver of the baby is large, accounting for 4.4% of the body weight. Because the structure of the baby's liver is not complete, so the baby's liver will:

- Easily move if there is a tumor or there is pleural fluid.
- The liver has many blood vessels, many cavities, and the cells are not fully developed.

Poor liver function, easy irritation when children have infections, poisoning and liver in children are also prone to fatty degeneration.

In order to protect the baby's health comprehensively, parents should have their children go for regular general health check-ups to detect health problems early, from which there are directions for early intervention and treatment.



The digestive system breaks food down into basic nutrients that can be used by the body. As food moves through the digestive tract, it's digested (broken down into parts and absorbed into the bloodstream). Certain organs (such as the liver, gallbladder, and pancreas) help with this digestion. Parts of food that can't be digested become stool. This is waste material that's passed out of the body.

Digestive system

The mouth takes in food and breaks it into pieces. It starts the process of digestion.

The esophagus moves food from the mouth to the stomach.

The stomach breaks food down into a liquid mixture.

The small intestine digests food further and absorbs nutrients. What's left is passed on to the colon as liquid waste.

The large intestine (colon) absorbs water, salt, and other minerals from liquid waste, forming a solid stool.

The rectum stores stool until a bowel movement occurs.

The anus is the opening where stool leaves the body.

The liver makes bile (a fluid that helps digest fat). It also breaks down nutrients and stores energy.

The gallbladder stores bile.

The pancreas makes enzymes that help with digestion.

The appendix is a small hollow structure that's attached to the large intestine. It has no clear function in the body. But it can become blocked and infected

Gastric motility is ruled by myoelectrical activity that consists of rhythmically occurring transmembrane potential variations, called slow waves, that are independent of the presence of motor activity. These waves that slowly travel through the GI tract are defined motor migratory complexes (MMCs) and occur every 2–4 h with the purpose of clearing the tract of undigested material, mucus, and debris . MMCs initially occur due to vagal input and the release of motilin in the duodenum. Their propagation, on the other hand, is coordinated by enteric neurons. MMCs occur in humans only during periods of fasting and in the small intestine as opposed to other species. Phasic contraction is related to a different kind of electrical activity, called electrical response activity, characterized by spikes superimposed on gastric slow waves. The origin of electrical activity is found on the greater curve, approximately in the proximal corpus, from where the slow waves propagate towards the pylorus.

Different motor patterns occur in the proximal and distal stomach. In the proximal stomach, receptive relaxation and accommodation occur, which are both mediated by neurons in the brainstem via vagal reflexes. The distal stomach exhibits different motor patterns during feeding and fasting. In the feeding state, the distal stomach grinds and mixes. Extrinsic neurons are not essential for this contractile activity, but it can be modulated by vagal pathways.

Intestinal motor activity is also correlated with gestational age and motor development, which is defined by phases I, II, and III of the migration of the motor complex between 37 GW and term age. In particular, the frequency of duodenal contractions, the number of duodenal contractions per impulse, and the peak intraluminal pressure of duodenal motility in preterm versus full-term infants are different . Clustered phasic contractions are more frequent but of shorter duration and lower amplitude; duodenal clusters are less common and antro-duodenal coordination is more immature in preterm infants.

A role of insulin on gut motility has also been supported by Shulman et al., who demonstrated significantly reduced gastric residuals within the first month in preterm infants treated with oral insulin compared to untreated peers.

The Enteric Nervous System

By 12 GW, the fetal colon has a dense neuronal network in the myenteric plexus with expression of excitatory neurotransmitter and synaptic markers. Instead, the markers of inhibitory neurotransmitters appear no earlier than 14 GW. However, electrical train stimulation of internodal strands did not evoke activity in the ENS of 12- or 14-GW tissues.

Onset of evoked electrical activity in the human fetal ENS appears at approximately 16 GW. Such activity appears to coincide with increases in gene expression of various ion channels known to modulate enteric action potentials. The temporal development of several neural subtypes and enteric glia occurs between 12 and 16 GW . The ENS consists of three parts: enteric neurons, enteric glial cells (EGCs), and ICCs. They form two major ganglionated structures and functional subunits—submucosal plexus (or Meissner's plexus) and myenteric plexus (or Auerbach's plexus). Meissner's plexus is located in the connective tissue of submucosa, and innervates muscularis mucosae, intestinal neuroendocrine cells, glandular epithelium and submucosal blood vessels, while Auerbach's plexus is located between the circular and longitudinal muscle layers and is associated with the contractility of the circular and longitudinal muscles .

Studies carried out on intestinal samples of mice show that ENS originates mainly from the cells of the vagal neural crest called neural crest precursor cells (NCC) that enter the foregut at 9 embryonic days and then migrate rostro caudally and colonize the entire intestine by 14 embryonic days.

Cdh19 is a direct target of Sox10 during early sacral NCC migration towards the hindgut and forms cadherin–catenin complexes which interact with the cytoskeleton in migrating cells . The migration phase is followed by the proliferation of NCCs which will form millions of ENS cells. The NCCs then assemble into groups (myenteric ganglia or submucosal ganglia) and then differentiate into a range of enteric neurons and glia cells and form complex neuronal networks necessary for controlled intestinal activity.

Diverse populations of fibroblast-like interstitial cells are present in the adult gut. Loss or dysfunction of these cells has been linked to a wide variety of GI disorders. This broad group of cells comprises various subpopulations of Kit-positive ICCs and fibroblast-like cells expressing PDGFRα. ICCs located at the level of the myenteric plexus (ICC-MY) mediate slow waves, the electrical events that time the occurrence of phasic contractions, while evidence is accumulating that ICC and PDGFRα-expressing cells located within and surrounding GI muscle bundles serve as intermediaries in both excitatory and inhibitory neuromuscular transmission.

Unlike enteric neurons and glial cells, ICCs do not arise from the neural crest, but have an embryonic development prior to the arrival of neural crest cells in the intestine. Several studies suggest that smooth muscle cells and ICCs are derived from a common mesenchymal precursor following an epithelial–mesenchymal transition process (EMT). Both ICC and CD34+ fibroblast-like cells derive from the coelomic epithelium, most likely from a common ancestor expressing the chlorine channel anoctamin-1 and smooth muscle actin alpha. Differentiation to the ICC phenotype during embryogenesis depends on cell signaling via the receptor tyrosine kinase, Kit. In recent studies on ontogeny of gastric electrical activity, myogenic control was found to be immature at birth and suggested a process of development from 1 week to 6 months.

The Microbiota-Gut–Brain Axis

During the early postnatal period, infants undergo consistent gut development, which is parallel and interdependent, even if not always synchronous, with brain development. In the first years of life, the gut experiences huge changes of the resident microbiota and a substantial maturation of both the enterocytes and of the ENS. Meanwhile, the brain and the central nervous system (CNS) grow rapidly, both in terms of brain volume and neural function.

The interdependency of the two developmental processes is mediated through the so-called gut–brain axis, which constitutes a bidirectional communication between the gut and the brain, made of several interrelated components . In recent years, the role of microbiota in the gut–brain axis has been studied extensively, so that the GBA is now commonly referred to as the microbiota-GBA (MGBA]. In this context, gut microbiota alterations have been directly linked to physical and mental health through a series of mechanisms which are yet to be fully elucidated.

The connection between gut and brain during early development involves both top-down and bottom-up mechanisms, with signals from the brain modulating GI functions, and GI-derived molecules influencing brain processes through different pathways. Even if the features of the MGBA in health and disease have been thoroughly described, the knowledge of the exact mechanisms through which the gut and the brain communicate in young infants is, at present, limited.

The mechanisms involved in the interplay between the brain and the gut include neural, endocrine, immune, and metabolic mediators.

Neural connections include the CNS, the ENS, and the autonomic nervous system (ANS). The ENS receives inputs from the brain and, in turn, provides ascending information through neural circuits. The ANS comprises sympathetic and parasympathetic nerves: the sympathetic system exerts mainly an inhibitory influence on the gut, while the vagus nerve (VN) appears to be able to sense hormones, cytokines, and metabolites from the GI tract, leading to afferent signals to the brain. The development and myelination of the VN is not complete at birth and continues until adolescence, with a peak in the myelination rate observed in the first months of life, when consumption of human milk, and human-milk-derived bioactive components, is the highest. The ANS is connected to the limbic system of the brain, whose main components are the hippocampus, the amygdala, and the limbic cortex, and which is responsible for a variety of brain processes in health and disease.

As for humoral components of the MGBA, they mainly consist in the hypothalamic–pituitary–adrenal axis (HPA), the enteroendocrine system and the immune system. Stress responses are modulated through the HPA, via the release of corticosterone, adrenaline, and noradrenaline. The enteroendocrine cells (EECs) in the gut produce GI hormones such as ghrelin, glucagon-like peptide (GLP-1), cholecystokinin, and peptide YY (PYY); these hormones regulate food intake and satiety and are also involved in the regulation of emotions and mood .

The resident immune cells in the brain, known as the microglia, act as a neuroimmune component of the MGBA, by finely tuning neurogenesis and synaptogenesis. The maturation and function of the microglia appear to be related to changes in the gut microbiota, and also influenced by SCFAs, which are end-products of bacterial fermentation of dietary fibers and resistant starch in the colon. Furthermore, immune signaling molecules, whose production is also driven by gut microbiota, can play a role in the MGBA, by binding to VN receptors or by crossing the blood–brain barrier. In this respect, recent studies have suggested a potential role of bacterial peptidoglycans (PGNs), which are components of the bacterial cell wall, released not only by exogenous bacteria, but also by the resident gut microbiota. It has been proposed that PGNs could enter the systemic circulation and reach the developing brain, where PGN sensing molecules are expressed abundantly during specific time windows of perinatal development, thus potentially exerting a direct effect on brain function and development.

Finally, a central role in the MGBA is played by metabolic mediators, including tryptophan metabolites such as serotonin (5-hydroxytryptamine, 5-HT), melatonin, SCFAs, and other neurotransmitters. 5-HT is involved in most branches of the MGBA; for instance, it acts as a neurotransmitter both in the CNS and ENS, and 5-HT receptors have a critical function in the HPA. The production of host 5-HT in the gut is regulated by microbiota, as indigenous spore-forming bacteria, derived from mouse and human microbiota, have been shown to promote 5-HT biosynthesis from enterochromaffin cells in the colon, thus impacting GI motility and homeostasis. SCFAs (acetate, propionate, and butyrate) are thought to influence gut–brain communication through different potential pathways, either directly or indirectly. Once produced by colonic fermentation, SCFAs can exert a direct effect on the intestinal mucosal immunity and can modulate the integrity and function of the gut barrier. Furthermore, by interacting with the EECs, SCFAs promote a direct gut–brain signaling through the secretion of gut hormones, such as GLP-1 and PYY, and other metabolic mediators such as γ-aminobutyric acid and 5-HT. In addition, they can induce systemic inflammation through differentiation of T regulatory cells and secretion of interleukins and can probably also act centrally in the CNS by modulating neuroinflammation .

There are several factors which could have a specific impact on the MGBA development in early life; one of the most relevant might be prematurity, as preterm birth interrupts the physiological growth and development of both the GI tract and the nervous system and leads to a certain degree of microbial dysbiosis. Despite that, at present there are no studies specifically designed to describe the unique features of the MGBA in preterm infants. In addition, nutrition during sensitive developmental time windows is thought to have a major impact on the microbiota-gut–brain crosstalk, either through an effect of single nutrients (e.g., milk fat globule membranes , human milk oligosaccharides, or through the well-known benefits of exclusive human milk feeding compared to other feeding sources.

Most studies aimed at describing the developmental-related characteristics of the MGBA have been carried out using rodent models, even if gut and brain development in rodents do not exactly reproduce human developmental patterns. For this reason, future preclinical research in the field of MGBA should be hopefully directed towards the use of animal models with more similar anatomy and physiology to that of humans (e.g., piglets). These models would allow a better understanding of the MGBA during early development and would pave the way for translating preclinical research into clinically relevant observations.

Beyond the contribution of studies based on animal models, the plausibility of the microbiota-gut–brain interplay also during early development is supported by clinical observations: so far, a limited number of studies has shown a correlation between specific microbial features in the gut during the early postnatal period and neurodevelopment, either in term or preterm infants.

The potential link between microbiota and neurodevelopment is particularly intriguing for preterm infants, as prematurity itself exposes them to both early dysbiosis and intrinsic risk of altered development. It has been suggested that the interplay between early dysbiosis and the gut–brain axis might lay the foundations for the altered neurodevelopment which is often observed in preterm infants experiencing necrotizing enterocolitis (NEC). Furthermore, a potential role of early alterations of the GMBA in later neurodevelopment has also been proposed for preterm infants not necessarily experiencing major neonatal complications such as NEC. For instance, in the French EPIFLORE population study, gut microbiota features in the first month of life in very preterm infants were associated with 2 year outcomes, even after adjustment for confounders. Similarly, in a small cohort of very low birth weight infants, a relationship between specific microbial characteristics during the first months of life (i.e., relative abundance of Bifidobacteria) and impaired neurodevelopment at 24 months corrected age was suggested .

Development of the Gut Microbiome

The intestinal microbiota is important in human growth and development. The human gut is home to trillions of microbial cells that bind in a symbiotic relationship to the host playing a vital role in both health and disease.

The relationship between microbiome and host is dynamic and many factors (such as genetic background, maternal diet prior to and during pregnancy, maternal microbiome, mode of delivery, gestational age, perinatal stress, infections during pregnancy and during the perinatal or neonatal period, feed type of neonates and especially of preterm infants, and other environmental factors such as temperature, humidity, pH, and oxygen levels in the tissues type) modulate the infants' microbiome constitution and its dynamic relationship with the host, which can be transformed from 'synbiotic' to 'dysbiotic' and life-threatening .

Of note, as illustrated in a recent narrative review, over the past decade several studies conducted on meconium have supported the fact that the fetus could be exposed to microbiota in utero, though previously the amniotic fluid and the placenta had been thought to be sterile. Placental colonization through a hematic route has been hypothesized as possibly responsible for the fetal colonization before birth.

Advances in high-throughput nucleotide sequencing technologies have enhanced gut microbiota research by investigating how bacterial communities develop over time, what factors affect them, and how they affect health and disease.

Gut Microbiome in Term Infants

The microbiota performs fundamental functions in human health, especially in childhood. The first year of life is considered a crucial window for any manipulation of the intestinal microbiota in order to promote proper development of the immune system and human well-being. Human first exposure to these microorganisms occurs at birth: once the baby is out of the womb, the microorganisms enter and settle in the intestine.

The TEDDY study, which describes the importance of the intestinal microbiota in the first years of life, demonstrated how the development of the microbiota in a full-term infant is influenced by breastfeeding, the type of birth, the geographical location, and the presence of siblings or animals in the home.

Other studies, on the other hand, are focusing on the impact that maternal factors, antibiotic use, host genetics, ethnicity, and even COVID-19 infection can have on microbiota development. Therefore, alterations of the intestinal ecosystem, known as dysbiosis, during this critical period of development are often associated with various kinds of pathologies.

Gut Microbiome in Preterm Infants

Prematurity at birth is a determining factor in the development of the intestinal microbiota. The premature baby, after birth, is admitted to NICU and thus exposed more to hospital-acquired bacteria than to familiar bacteria . Furthermore, the clinical practices to which these small patients are exposed, e.g., ventilation, artificial feeding, and antibiotic reception, alter the normal development of the microbiota. Moreover, pre-term infants have immature GI tracts and naïve immune systems.

Several studies have shown how this immaturity and diversity of the microbiota affects the development of intestinal function and anatomy of intestinal villi, crypts and of the intestinal barrier, causing several serious disorders in the premature newborn such as late-onset sepsis (LOS) and NEC. Substantial efforts have been made over the past few decades to define the microbial characteristics of NEC and LOS, and compelling data have associated both conditions with intestinal dysbiosis.

Human milk has a protective role against both NEC and LOS as it confers immunological benefits to the baby and provides nutrient-specialized microbes that likewise enrich the baby's immune system. Specifically, human milk provides nutrients such as oligosaccharides, essential for the growth of bifidobacterial-type bacteria. Bifidobacteria have been shown to possess immunomodulatory and anti-inflammatory properties by strengthening the intestinal barrier and reducing the risk of NEC. Premature babies have low levels of these bacterial species and are more exposed to the risk of NEC. Safety and efficacy of probiotic administration to modulate early gut microbiome in preterm neonates is being investigated . Gaining a deeper understanding of the microbiome using relevant methodology will enable the exploration of new targeted therapeutic strategies in preterm disease as well as in a range of other pathologies.

Conclusions. The intestine represents a vast interface between our internal and external environments. The second and third trimesters of pregnancy are crucial to the anatomical and functional development of the GI tract and the related digestive functions. Following premature birth, the immaturity of the digestive and absorptive processes and of the GI motility represent a critical challenge to the establishment of adequate enteral intakes in the preterm population and are often involved in the development of premature-related GI complications, ranging from food intolerance to NEC. In the context of gut immaturity, the choice of the optimal source of nutrition for preterm infants is fundamental: keeping mother's own milk in mind as the magic bullet for preterm infants' nutrition, future research should continue to address the potential role for mother's own milk substitutes, such as donor milk and formula, for preterm infants. Specifically, the potential effects of donor milk treatments such as freezing and pasteurization on milk bioactive properties should be further investigated, while infant formula research should be oriented at developing a milk substitute which would be nutritionally adequate and, at the same time, easy to tolerate and digest for these immature infants.

Moreover, there is much evidence that microbes residing in the intestinal tract play important roles in the ontogenesis of the immune system and interact with the gut and central nervous system. The interplay between GI development and microbial colonization is dual: while the immature anatomical and functional features of the preterm gut predispose to an abnormal intestinal microbial colonization, the latter may interfere with the functional, immune, and neuronal development of the GI tract. It should be constantly kept in mind that the perinatal period most likely corresponds to a critical moment in which the "set points" are impressed; it is therefore necessary to learn more about normal and healthy colonization patterns in infants to promote these patterns and avoid perturbations that result in disease throughout life.

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