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The relationship between gut microbiota and neonatal sepsis is an inherent link

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Abstract: Currently, sepsis remains a global burden that causes high morbidity and mortality rates worldwide. The incidence of sepsis has been increasing lately, particularly among vulnerable groups of children, especially neonates. This poses a significant challenge, particularly for preterm infants. The gut plays an important role in human health and development, with the gut microbiome being one of the most substantial factors. The development of gut microbiota is crucial for children's growth, starting from the intrauterine phase, during delivery, and after birth. Many factors influence changes in gut microbiota, including maternal and neonatal factors. These changes can trigger dysbiosis, which may subsequently lead to sepsis and increased mortality. This review explores the development of gut microbiota from the intrauterine phase to the neonatal period and its relationship with the occurrence of neonatal sepsis.

Keywords: *Gut, Intestinal, Microbiota, Neonatal, Relationship, Sepsis.*

1. Introduction

Sepsis is a potentially fatal organ failure caused by an abnormal host response to infection [1]. Neonatal sepsis is associated with high morbidity and mortality [2] accounting for between 400,000 and 900,000 fatalities each year [3]. Globally, the incidence of neonatal sepsis is about 2,022 cases every 100,000 live births, with 11% to 19% death rate [4]. Preterm infants and very low birth weight (VLBW) are very susceptible to neonatal sepsis [4]. Neonatal sepsis is commonly defined as either early-onset sepsis (EOS), which appears within the first 72 hours of life, or late-onset sepsis (LOS), which appears more than 72 hours after delivery [6]. Neonatal sepsis is still difficult to diagnose and treat on time [5-7].

The first few years of life are crucial for developing the gut microbiota [8]. However, changes in the gut microbiota can occur as a result of a variety of life events, resulting in gut dysbiosis, which has been linked to developmental disorders and neonatal sepsis [9]. This review focuses on neonatal gut microbiota growth and its relationship with dysbiosis and sepsis in neonates.

2. Intrauterine Gut Microbiota

During pregnancy, the intrauterine environment is a vital point of interaction between the mother and the growing fetus, making it a suitable target for researchers studying fetal programming mechanisms [10]. A rising number of studies have discovered that the microbiome at birth is influenced by host genetics, the prenatal environment, and the delivery process [11]. The presence of a microbiome in utero healthy pregnancy is an interesting topic. The intrauterine environment was believed to be sterile historically. However, recent studies using material sequencing techniques have

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demonstrated the presence of commensal bacteria in the uterus and healthy placenta of both human and animal models [12-16].

The human placenta has a unique microbiome, which was discovered using whole genome sequencing [13-16]. However, the species discovered in various investigations are inconsistent. Several studies have discovered that the placental microbiome is quite similar to the oral microbiome, with *Escherichia coli*, *Prevotella tannarae*, and non-pathogenic *Neisseria* being the most common [13, 15]. Others discovered that bacterial populations in the placenta were more like those in the vagina [14]. Recent research has shown that gut microbiota and its metabolites play important roles in gut-systemic metabolic concession, which may influence general metabolic development and the immune system in early life [17, 18].

3. Gut Microbiota Changes During the Birth Process

The mode of delivery has an important role in shaping the composition of neonatal microbiota [19]. Cesarean section (CS) is a life-saving obstetrical operation for both the mother and the infant [20]. *Lactobacillus reuteri* and *Lactobacillus rhamnosus* are some of the probiotics identified in the birth canal. Compared to CS, infants who were born by vaginal delivery (VD) have more beneficial bacteria in their mouth, nasal cavity, skin, and other regions. The bacterial populations in infants born by VD are similar to those in the maternal vagina. Studies have found that the CS infants' gut flora differs significantly from VD infant's.

Bacterial colonization in CS newborns resembles those found on their mother's skin [21]. The manner of dispersion may alter microbial development, changing normal physiology or disease vulnerability [22]. It was also shown that vaginal microbial transmission aids neonates in developing their early gut microbial structure [22-24]. Neonatal gut microbiota maturation is critical for early microbiota development [25, 26]. Previous studies demonstrated that the abundance of *Escherichia*, *Bifidobacterium*, and *Lactobacillus* in CS-delivered newborns was lower than that of vaginally delivered neonates [27-29]. In contrast, numerous pathobionts, including *Staphylococcus* and *Klebsiella*, have dropped over time [30].

The connection between CS delivery and gut flora is being more widely investigated. Because maternal birth canal bacteria are absent in CS-born infants, their gut microbial compositions differ [31]. Cesarean-born infant's microbiomes differ from those of vaginally delivered infants, and they are more likely to develop diseases. Vaginal microbiota transfer (VMT) to neonates may correct CS-associated microbiome disruptions [32].

It was assumed previously that the fetus develops in a sterile environment and that gut microbiota colonization happens after delivery [33]. In recent years, however, tests have proven that fetal membranes, amniotic fluid, placenta, umbilical cord blood, and fetal feces during a normal pregnancy contain germs [34] and that intestinal microorganisms can be passed vertically from mother to fetus in utero [35]. Prenatal maternal bacterial exposure influences the fetal stool microbiome [36]. The microbial makeup of newborn feces at seven months of age was very comparable to fetal feces, showing that fetal gut microbes play a role in the early colonization of human gut bacteria [37].

4. Gut Microbiota Changes During the Neonatal Period

The human gut microbiota contains an extraordinarily diversified microecology, with a population of approximately 1,014 healthy humans, or 10-20 times the total number of cells in the human body [38]. The newborn period is a pivotal phase of dynamic change for the gut microbiota, influenced not only by characteristics such as gestational age, birth weight, mode of delivery, feeding (type of milk), but also oxygen support, medical devices, timing of antibiotics or other drug administration, and health care system [9, 39, 40].

The gut microbiota develops rapidly from birth, and its development throughout the first few years of life can have a long-term impact on an individual's health. However, various circumstances can induce gut flora alteration, resulting in dysbiosis, especially in preterm newborns. Current research on adults

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suggests that the gut microbiota regulates the gut and has multifaceted effects on distant organs; these pathways are commonly referred to as the gut-organ axis. Imbalances in the gut microbiota can contribute to the development of various diseases [41].

Preterm infants are babies who are born before 37 weeks gestation. The gut microbiome varies significantly between preterm and term newborns [42]. Preterm newborns develop gut microbiota later than term infants and have lower gut microbiota richness and diversity and levels of pathogenic bacteria [43]. Previous research has characterized the gut flora of preterm infants there is a significant decrease in *Firmicutes* and an increase in *Proteobacteria* [45]. Preterm infants showed higher levels of *Bacteroides*, *Lactobacillus*, *Enterobacter*, *Klebsiella*, and *Enterococcus* than mature neonates, although lower abundance of *Bifidobacterium*, delayed colonization, limited microbiota diversity, and a longer time to peak abundance [44, 45].

The gut microbiome of preterm newborns was identical to that of healthy infants at birth, but it changed into dysbiosis weeks later, with an increase in *Proteobacteria* and a decrease in *Firmicutes*. The study found that septic very low birth weight (VLBW) preterm infants had decreased gut microbial diversity at delivery compared to non-septic preterm infants and term infants [46].

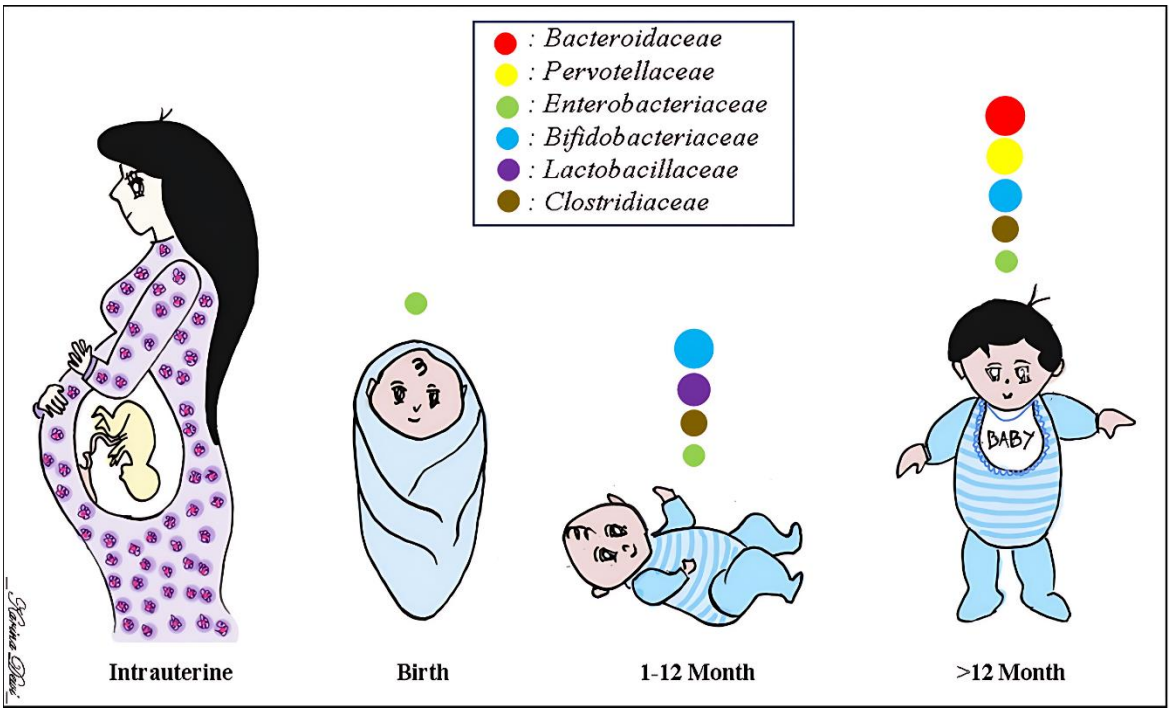

Figure 1.
Composition changes of the child's gut microbiota over time.

Neonates in intensive care units (NICU) are a distinct population with underdeveloped systems and a developing microbiome [47]. Early research has indicated that these infant's gut microbiomes are frequently similar to bacteria found in the NICU. Preterm infants in the NICU are a unique population with underdeveloped organs, a high risk of infection, numerous arduous operations, and separation from their moms, demanding special care and study [48].

Proteobacteria dominated the gut flora of preterm newborns at various time intervals, followed by *Firmicutes*, *Actinobacteria*, *Tenericutes*, and *Bacteroidetes*. *Proteobacteria*'s relative abundance first declined, reaching a low on day of 14, before rising. *Firmicutes* have similar patterns in relative abundance to *Actinobacteria* but opposite tendencies to *Proteobacteria*. The gut microbiota and metabolic-functional pathways of preterm newborns in the NICU changed from one to sixty days after birth, with the major

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gut microbiota originating from *Aspergillus* and *Pseudomonas*, whereas the relative abundance of *Bifidobacteria* was low. Preterm newborns' gut microbiomes are affected by their feeding patterns [49] [50].

5. Dysbiosis, Translocation, and Neonatal Sepsis

Dysbiosis in the gastrointestinal tract (GIT) is associated with neonatal sepsis. It is defined as (1). Decrease in microbial diversity at the time the baby is delivered or during developmental attainment, (2) Increase in *Proteobacteria* with a decrease in *Firmicutes*, and (3) The gut microbiota evolution disrupted from facultative to obligate anaerobic dominance. Bacteria rapidly infect infants' gastrointestinal systems at birth. The first few years of life are crucial for the development of the gut microbiota. However, altering gut microbiota growth in newborns might cause gut dysbiosis, which is characterized by pathogenic bacterial over-colonization and delayed or unsuccessful maturation toward increased microbial diversity and *Firmicutes* dominance. Infants with intestinal dysbiosis have a higher chance of developing sepsis. Pathogenic bacteria can enter the gut and cause sepsis by translocation [50, 51].

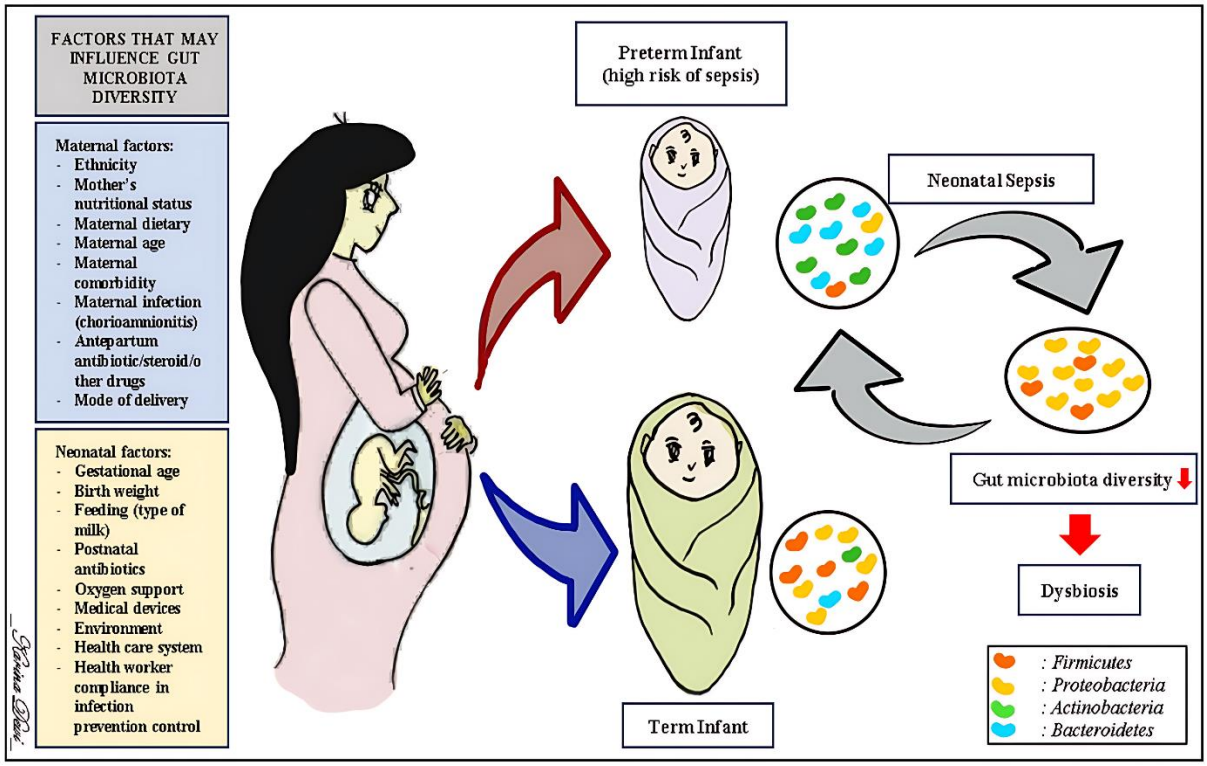

Figure 2.
Dysbiosis affects the incidence of neonatal sepsis.

Gut dysbiosis may precede infant sepsis, but the association is still poorly understood [52]. This microbiota and the gut have a symbiotic relationship, which helps to maintain gut homeostasis, mature gut function and structure, facilitate nutrition and metabolism, provide antimicrobial protection, and modulate the immune system [52]. In neonates, the gut is immediately colonized by bacteria after birth, and the gut microbiota grows dramatically throughout the first few years of life. Initially, the gut microbiota is low diversity and primarily formed of *Proteobacteria* and *Actinobacteria*; however, by the age of 2-3 years, the gut microbiota transforms to an adult-like composition, with *Firmicutes* as the major phylum [50]. However, the makeup of the gut microbiota can be influenced by a variety of internal and external stimuli, resulting in dysbiosis. Recent research revealed that gut flora changing can caused by

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some factors such as tight junction proteins disruption, local immunity alteration, and decreased of protective secretions. These factors increase vulnerability to some illness such as necrotising enterocolitis (NEC) and sepsis [53].

Preterm infants with LOS demonstrated reduced gut flora diversity at birth, with a higher incidence of *Staphylococcus* preceding LOS. The longer the antibiotic duration, the lower gut microbes diversity and aided in pathogen-dominated microbiota development [54]. Preterm infants ≤32 weeks with LOS most likely to experience dysbiosis, characterized by decreased gut flora diversity in the first two weeks leading up to LOS, with an increase in *Proteobacteria* and decrease in *Firmicutes*. *Bifidobacteria* levels were consistently lower in LOS preterm infants [55].

Late onset of sepsis infants experienced gut dysbiosis characterized by lower gut microbial diversity at birth and abnormal development toward an increase in the *Proteobacteria* and decrease in *Firmicutes* [56]. Late onset of sepsis was associated with abnormal microbiota, as seen by the abundance of *Enterobacteriaceae* and *Staphylococci* in a week prior to LOS, it shows dysbiosis was defined as a failure to grow into a preponderance of obligatory anaerobes [57]. Stewart et al. found similar results, nothing that the causal pathogen's genus was numerous in the intestine prior to LOS and that a relative abundance of *Bifidobacterium* protects against LOS [58]. Liu et al. similarly found that LOS was dominated by the *Klebsiella* [59]. Graspeuntner et al. conducted a comprehensive prospective study that included LOS preterm infants and healthy preterm infants. They discovered that preterm infants had gut dysbiosis prior to LOS onset, with bacilli predominance and increased of microbial diversity in the healthy group, but decreased microbial diversity in the LOS group [60].

Bacterial translocation could explain how gut dysbiosis can cause neonatal sepsis. The idea that the gut is a reservoir for bacteria and that sepsis began first hypothesized in the 1940, when live bacteria during peritoneal irrigation in dogs with hemorrhagic shock were identified [61]. Berg and Garlington [62] proposed the bacterial translocation concept which describes the transfer of live, the original intestinal bacteria from the GIT to typically sterile tissues such as mesenteric lymph nodes and other internal organs [62]. This concept also includes the transmission of chemical inflammatory mediators produced by the intestinal wall or bacterial products that cross the gut mucosal barrier and cause systemic symptoms [63, 64]. This term also refers to the transfer of commensal organisms from one body location to another, which may cause health problems, through various interaction mechanisms such as the oral-gut axis, gut-blood axis, oral-blood axis, and skin-blood axis [65].

The gut bacterial translocation could explain why dysbiosis causes neonatal sepsis. The intestinal goblet cells produce mucous coating intestine, which contains antimicrobial peptides, degraded mucin, and other microbiota products, serves as the first line of defense against bacterial translocation. However, mucin's capacity to prevent bacterial translocation in newborn enterocytes may be less efficient than in adults [66, 67]. Furthermore, the intestinal epithelial junction complex, consist of tight junctions, defends the intestinal barrier in numerous ways and is crucial in preventing bacterial translocation [68]. Submucosal macrophages consume microorganisms that have crossed the mucous and epithelial barriers, but if the intestinal macrophages are faulty, as they can be in VLBW children, microorganisms can enter the systemic circulation via the submucosal through transcellular or paracellular routes. Bacterial toxins, such as flagellin, endotoxins, and exotoxins disrupt tight junctions in the paracellular pathway, whereas bacteria enhance the transcellular pathway via membrane receptors [19, 69].

Generally, identical strains growing together from two body locations can be considered to be the result of bacterial translocation, with the body location where the strain is most frequently found being the source of the translocation. As a result, cultivating the identic bacterial strains from stool and blood samples can only infer that the illness is caused by the causal pathogen's translocation in the stomach. However, this conclusion is not accompanied by evidence of temporal causality, making it impossible to determine whether the causative pathogen colonized the gut before the onset of sepsis or was a result of bacteremia [58].

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A few studies have shown that gut bacteria can cause neonatal sepsis. Carl et al. used whole-genome sequencing to discover that the causal microorganisms were present in the stool samples of LOS infants before the onset of the disease, implying gut microbiota colonization prior to LOS. The results include strains of *Streptococcus agalactiae*, *Serratia marcescens*, *and Escherichia coli* [56]. This was determined utilizing specially developed paired strain-specific primers based on whole-genome sequencing of harmful bacteria. The four organisms responsible were *Klebsiella pneumoniae*, *Escherichia coli*, *Staphylococcus aureus*, and *Staphylococcus epidermidis*. A prospective cohort study compared the fecal microbiota makeup of preterm infants with and without sepsis. The bacterial isolates that cause neonatal sepsis had their genomes sequenced. Polymerase Chain Reaction (PCR) was used to confirm the bacteria's translocation from the intestine to the bloodstream. The same bacterial strain could spread horizontally, infecting other newborns [46]. This is what can then explain the possibility of translocation of intestinal bacteria into the bloodstream. This is what then links between dysbiosis due to gut microbiota's imparity and the occurrence of neonatal sepsis.

6. Conclusion

This review discusses how gut microbiota develops while the baby is still in the mother's womb until birth and develops during the neonatal period. The high rate of prematurity certainly increases the incidence of neonatal sepsis, which is related to the incidence of gastrointestinal dysbiosis. This is very important as a basis for further research in an effort to modulate gut microbiota to optimize the management, so that morbidity and mortality rates in neonatal sepsis can be suppressed.

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Institutional Review Board Statement:
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Currently, sepsis is still a global burden that causes high morbidity and mortality rates throughout the world. The incidence of sepsis has been increasing lately, especially in a vulnerable group of children, which is neonates. This will be a big challenge, especially in preterm infants. The gut plays an important role in human being and development. One of the most substantial is the whole gut microbiome. The development of gut microbiota is very important in children's development, starting from intrauterine, at delivery time, and after birth. Many factors influence changes in gut microbiota, including maternal and neonatal factors. This can trigger dysbiosis condition and subsequently cause sepsis and mortality. This review explores the development of gut microbiota from intrauterine to the neonatal period and its details with the occurrence of neonatal sepsis.

Transparency:
The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

Conflict of Interest:
The authors declare no conflicts of interest regarding the article's publication.

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K.P.D. designed the study, conducted the statistical analysis, and produced the original manuscript; R.E. and I.G.M.R.G.R. both contributed to the study's conceptualization and critical review. All authors have understand and approved the published version of the manuscript.

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