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Long-term effects of antibiotics administered during cesarean on neonatal health outcomes

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ABSTRACT

This review explores the intricate relationships between antibiotic use during cesarean section (CS) and its long-term effects on neonatal gut microbiota and subsequent health outcomes. The human microbiome, especially the gut microbiota, is a complex ecosystem that plays a crucial role in health and disease. It is established early in life and is influenced by numerous factors including genetics, diet, lifestyle, and particularly, perinatal antibiotic exposure. The development of the gut microbiota starts before birth, and the mode of delivery significantly impacts its initial composition. Infants delivered by CS exhibit differences in their microbiota, characterized by reduced diversity and lower levels of Bifidobacteria and Bacteroidetes compared to those born via vaginal delivery. This alteration can be attributed to the lack of exposure to the maternal vaginal microbiota and the widespread use of prophylactic antibiotics during CS. These antibiotics cross the placenta and affect the fetal gut microbiome during a critical period of immune and metabolic programming. Studies highlight that early antibiotic exposure is linked to an increased risk of developing conditions such as obesity, asthma, and inflammatory bowel disease later in life.

KEY WORDS: Antibiotics, cesarean section, neonatal microbiota, gut microbiome, perinatal antibiotic exposure.

INTRODUCTION

Over time, human and microbial genomes have co-evolved, intertwining their metabolisms and survival mechanisms inseparably. The gut microbiota consists of a complex assembly of bacteria, viruses, and some unicellular eukaryotes. The term 'microbiota' refers to all microorganisms found in humans, whereas 'microbiome' encompasses the genomes, gene products, and metabolic activities of these microorganisms [1, 2]. Humans are superorganisms, composed of 10% human and 90% microbial cells [1, 3]. While the human genome contains around 35,000 genes, there are over two million bacterial genes, making the bacterial genome 150 times larger than the human genome. This intertwined existence of human and microbial genomes is known as the hologenome [4]. The surface area of the gut bacteria is 400 m², and they weigh approximately 1.5-2 kg (5,6). The gut microbiota is comprised of

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100 trillion (10^{14}) cells, including bacteria, viruses, and some unicellular eukaryotes [7].

The gut microbiota is unique like a fingerprint, and each individual has a mix of shared and unique microbial composition and distribution. The microbiota varies based on a multitude of endogenous and exogenous factors such as geographic location, genetic makeup, mode of birth, age, lifestyle, diet, antibiotic use, and past illnesses. For instance, the abundance of Firmicutes bacteria increases from infancy to old age, while Bacteriodetes decreases. High protein, red meat, and animal fat intake affect the Bacteroides genus, whereas a carbohydrate-rich or vegetarian diet impacts the Prevotella genus. Studies have shown that a diet rich in resistant starch affects the Ruminococcus family. The use of antibiotics causes temporary or permanent unhealthy changes in the microbiota, depending on the antibiotic class and the life stage at which they are used [1, 2, 7].

The microbiota begins to form during birth from bacteria transferred from the mother and the environment [7]. Until recently, the neonatal flora was considered sterile, but studies have shown the presence of a microbiota in meconium, originating from the mother's microbiota. This contributes to the shaping of the neonatal microbiota before birth (4). During birth, the newborn encounters numerous microorganisms, forming the gastrointestinal system's microbiota. This unique neonatal microbiota is influenced by various internal and external factors, including the mother's diet, use of antibiotics and probiotics during pregnancy, elective cesarean section (CS), and the absence of physiological stress and certain hormones [8, 9]. In normal vaginal delivery (VD), the newborn's microbiota is formed by the mother's genitoüriner system microorganisms, whereas in CS, it resembles the skin flora. Jakobsson et al. demonstrated that CS birth reduces the diversity of the gut microbiome and results in a lower abundance of Bacteroidetes [11].

Knowledge about the effects of infant gut microbiota colonization on health and disease in later life is rapidly increasing [12]. A blueprint for the final composition of the microbiota is established during early infancy. During this critical window, commensal microorganisms interact with the mucosal surface and are responsible for programming the immune system [13]. While postnatal events are thought to have the greatest impact on microbiome formation, recent evidence suggests that prenatal factors also play a role in the development of the infant microbiome [14]. The gut colonization of the newborn is influenced by numerous perinatal factors such as the mode of birth, type of feeding, gestational age, and the newborn's use of medications, especially antibiotics [15]. It is also believed that antibiotics used by the mother influence this colonization process [16].

Prophylactic antibiotics given before surgical incision during CS cross the placenta and expose the fetus to antibiotics at a time when the human gut is being colonized by microbes. Newborns delivered by CS are associated with a higher risk of obesity, and it is unclear how much of this association is due to perinatal antibiotics given during birth. Studying the meconium microbiome can offer insights into how intrauterine exposures might affect the development of the earliest gut microbiome.

This research aims to delve into the long-term effects of antibiotics administered during cesarean sections on neonatal health outcomes. By examining the disruptions caused to the gut microbiota and their implications, this study seeks to illuminate the pathways through which early microbial imbalances impact the development of various health conditions.

General Information

Microbiota

Over time, human and microbial genomes have co-evolved, merging their metabolic activities and life-sustaining features inseparably. The gut microbiota is a community of microorganisms consisting of archaea, bacteria, viruses, and fungi [17, 18]. 'Microbiota' refers to all the microorganisms present in humans, while 'microbiome' refers specifically to the genome of these microorganisms [4]. The human body, composed of 10% human cells and 90% microbial cells, is considered a superorganism. The total number of genes in the microbiota is approximately 150 times greater than the total number of human genes [1]. It is estimated that the gut microbiota of an adult individual contains about 10141014 bacterial cells, with 500 to 1000 different bacterial genera, and weighs approximately 1.5-2 kg [6]. Today, the gut microbiota is recognized as an 'organ' that significantly impacts human health and physiology. Furthermore, the microbiota is situated within the gut-brain axis, linking neural, immune, endocrine, and metabolic pathways bidirectionally [19].

The Human Microbiome Project was first initiated in 2007 by the National Institutes of Health (NIH) in the United States. This project has contributed to a better understanding of the healthy composition and functional characteristics of the gut microbiota and has shed light on the identification of species and genes of microorganisms in the microbiota using metagenomic methods, helping to characterize our microbiota [1]. Despite these developments, many areas still remain unclear and in need of research.

Microbiota can be found on nearly all surfaces of our body that are exposed to the external environment. The gastrointestinal, respiratory, and urogenital systems, along with the oral cavity and skin, are regions where microbiota is present. The composition of the microbiome in the esophagus and stomach differs from that in the colon. Due to its large surface area and richness in nutrients for microorganisms, the gastrointestinal system hosts the most intense bacterial colonization, with greater species diversity and a higher number of contents per gram [20]. The colon is the part of the body where flora is most densely populated, containing as many microorganisms as there are human cells in the entire body [4].

The gut microbiota profile is established by collecting fecal samples from individuals and isolating DNA from these samples. The identification, isolation, and counting of the majority of microorganisms found in the gastrointestinal system using culture-based techniques are difficult and laborious processes. As most microorganisms in the gut are anaerobic, only about 10-25% of the microbiota can be isolated using culture-based methods. With advancements in anaerobic culture methods, dominant genera such as Bacteroides, Clostridium, and Bifidobacterium have been identified. The drawbacks of these methods include the time they take and the difficulty of examining the cultural characteristics of various colonies on a Petri dish [21].

Recently, advancements in microbiota research methods have allowed for the detailed and comprehensive characterization of microbiota content. Currently, in addition to culture-independent molecular microbiological methods such as polymerase chain reaction (PCR) and 16S ribosomal RNA (rRNA) for determining microbiota, methods combined with PCR, fluorescent in situ hybridization (FISH), and gel-based methods are utilized [22]. Studies using these new diagnostic methods have detected and classified more comprehensive microbiotas. The metagenomic sequencing method enables a comprehensive definition of the

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collective genome of the gut microbiota and, consequently, the functional capabilities of the existing gut bacteria [6]. Metagenomic analysis is conducted using 16S rRNA-based sequencing of bacterial genes and bioinformatic analysis. There are highly conserved, hypervariable regions in the 16S rRNA gene region that facilitate bacterial species differentiation, and this 16S rRNA consists of these 9 hypervariable regions (V1-V9) [5]. Based on these regions, bacterial gene sequencing is created, and bioinformatic analysis is performed based on the libraries created. The gut microbiota is normally in a state of balance. The balance among bacterial groups directly impacts human health. An abnormal composition and function of the microbiota are known as "dysbiosis." Changes in microbiota diversity that affect host metabolism reduce the abundance of beneficial bacteria while supporting the growth of potentially pathogenic microorganisms [23-24]. Research has shown that microbial imbalance disorders in the microbiota are associated with numerous health issues such as obesity, diabetes, hypertension, cancer, and irritable bowel syndrome [22]. The ratio between the Firmicutes and Bacteroidetes groups is often studied, and this ratio, especially related to the type of diet (Western or vegetable-heavy), has been reported. For instance, changes in the Bacteroides and Firmicutes ratio in obesity can promote fat storage, increase energy harvest from foods, and reduce energy expenditure [24].

Formation of the Microbiota

While the gut microbiota shows individual variations, it possesses unique characteristics like a fingerprint specific to each person. During this process, the microbiota changes depending on endogenous and exogenous factors that vary throughout an individual's life. Factors such as mode of birth (CS-VD), diet, age, genetic makeup, lifestyle, geographic location, antibiotic use, medication use, prebiotics, probiotics, and past illnesses all influence the formation and shaping of the microbiota [18].

Early studies knew that the microbiota was formed during birth. However, today, there are scientific proofs that bacteria exist in the intrauterine environment and colonization begins in the intrauterine period [8]. It is thought that bacterial colonization can occur with meconium colonization during the intrauterine period. Studies based on 16S rRNA sequencing have reported that genera such as *Escherichia, Shigella, Enterococcus, Leuconostoc, Lactococcus,* and *Streptococcus* are abundant in the first meconium [25]. The bacteria in the meconium are passed from the mother's microbiota to the newborn. This contributes to the shaping of the neonatal microbiota during the prenatal period [4].

It is believed that one of the most influential factors on the microbiota is the mode of birth. During birth, the newborn encounters many microorganisms in the vagina, thus forming the gastrointestinal system microbiota. This microbiota formed in the newborn is influenced by many internal and external factors. It has been reported that the early colonization patterns of babies born by CS are very different from those born by VD. It has been shown that the first microbiotas of infants are primarily structured according to their mode of birth and that the differences in bacterial populations in the baby's intestines resemble the type of microbiota encountered at birth. Post-birth 16S rRNA sequencing data show how much the baby's gut microbiota resembles the mother's vaginal or skin microbiota, depending on the mode of birth. The intestines of newborns delivered by VD are initially colonized by bacteria from the mother's vagina, such as *Lactobacillus* and *Prevotella*. In contrast, the intestines of newborns delivered by CS are colonized by bacteria from the mother's skin flora, such as *Streptococcus, Corynebacterium,* and *Propionibacterium* [8, 26]. It is known that this initial colonization affects human health throughout life [4, 26]. Additionally, the analysis of fecal samples from children 3 days after birth using temperature gradient gel electrophoresis has shown significant differences in the bacterial populations in the intestines of babies born by CS and VD [15]. Babies born by CS host fewer *Bifidobacterium* and *Bacteroides* species compared to those born by VD. In a study by Penders et al., examining factors affecting the composition of the gut microbiota during early infancy, researchers analyzed the fecal microbiota of 1,032 Dutch babies at one month old and found that babies born by CS had fewer *Bifidobacterium* and *Bacteroides* compared to those born by VD, while being more frequently colonized by *C. difficile*. They also found that the most important determinants of gut microbiotic composition in infants were the mode of birth, type of feeding, gestational age, hospitalization of the baby, and antibiotic use, and that term babies born at home by VD and fed exclusively with breast milk had the most "beneficial" gut microbiota [15]. Furthermore, Jakobsson and colleagues have reported that the gut microbiota of 24-month-old babies born by CS is less diverse than those born by VD. Researchers have speculated that this decrease in diversity could be due to delayed colonization by *Bacteroidetes* in the gut, as some babies born by CS did not show signs of *Bacteroidetes* colonization until the age of one [27].

Along with the variations in gut microbiotas between babies born by VD or CS, various immunological disorders associated with the mode of birth have been linked. Bager and colleagues have stated that birth by CS, independent of a parental history of inflammatory bowel disease, is associated with a higher risk of developing inflammatory bowel disease between the ages of 0 and 14. Decker and colleagues found that children born by CS have an increased risk of developing celiac disease [25]. Blustein and colleagues, in their study involving 10,219 children, 926 of whom were born by CS, found that birth by CS was consistently associated with adiposity at 6 weeks and that this association was even stronger if the children were born to obese mothers. They also reported that these children were 1.83 times more likely to be overweight or obese by the age of 11 [26].

Diet

The diet also affects the gut microbiota. Recently, it has been reported that the gut microbiotas of babies fed breast milk and those fed formula milk differ. Babies fed formula milk have a different structure of gut microbiota compared to those fed breast milk. The microbiota of breastfed babies is dominated by *Bifidobacterium* and *Lactobacillus*, while the gut microbiota of formula-fed babies consists of *Enterococcus, Enterobacteria, Bacteroides, Colostridia*, and other anaerobic *Streptococcus* [4, 7]. In a study evaluating the development and differences of gut flora in breastfed and bottle-fed newborns, on the 6th day of the newborns, the dominant organisms in the feces of breastfed babies were bifidobacteria outnumbering enterobacteria by a 1,000:1 ratio, while in formula-fed babies, the dominant organisms, enterobacteria, outnumbered bifidobacteria by about 10:1. At one month old, bifidobacteria were the most common organisms in both groups, but their number in the feces of bottle-fed babies was about one-tenth of that in breastfed babies. In a study by Penders et al., it was reported that babies fed only with formula milk were more frequently colonized by *E.coli, C.difficile, Bacteroides,* and *Lactobacilli* compared to breastfed babies [15].

Diet is another important factor in the formation of microbial abundance and diversity. Nutrients ingested with the diet are broken down by enzymes in the digestive system and absorbed from the intestines. Fibers that cannot be broken down by enzymes contribute

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to the microbiota. In those who consume fruits, vegetables, and fiber-rich foods, species from the Firmicutes group (such as *Ruminococcus bromii, Roseburia*, and *Eubacterium rectale*) that help metabolize indigestible carbohydrates are more dominant [27]. In those who consume animal foods, the Firmicutes group decreases, and species resistant to bile secretions such as *Alistipes spp.* and *Bacteroides spp.* from the Bacteroidetes group and *Bilophila spp.* from the Proteobacteria group increase [16-17]. In a study investigating the relationship between diet and microbiota, it was found that the gut microbiotas of those who consume a red meat-heavy diet differ from those who consume a vegetable-heavy diet. In those who eat red meat, nitrogen-assimilating genes are more abundant, while in those who eat vegetables, bacteria suitable for the complex and laborious structure of plant polysaccharides are reported [4]. In a study by Filippo and colleagues, it was found that the microbiotas of African children fed a fiber-rich and plant food-based diet had more of the genus *Prevotella*, while Italian children fed an animal food-based diet had a higher amount of *Bacteroides* species [25].

Age

Initially characterized by relatively low diversity and instability, the microbiome rapidly develops in early life. The changes in the microbiota during infancy and early childhood are the periods with the most intense changes in the microbiota. The microbiota found in a baby's intestines can be affected by stages of development such as whether the pregnancy is full-term or premature. Other factors include the mother's weight, whether she is overweight or malnourished, and antibiotic use. The most dramatic changes occur during infancy because the plasticity and complexity of the baby's microbiota are critically important in maintaining homeostasis in a baby's immune system, reflecting the baby's health in later stages of life to a large extent [28].

Despite the presence of bacteria in the meconium, colonization in the newborn intestine begins with birth. In babies born by VD, colonization initially occurs with species found in the vaginal microbiota, while in babies born by CS, colonization initially occurs with skin microbes. In the early period of life after birth, the proportion of Bifidobacteria increases and the proportion of anaerobic organisms decreases in the microbiotas of babies fed with breast milk compared to those fed with formula [4]. The microbiome changes again with the introduction of solid foods, and by about age 3, children have a relatively stable gut microbiome that is 40-60% similar to that of adults [4-6].

Age and Its Influence on Microbiota Composition

As individuals age, the proportions of Bifidobacteria, Firmicutes, and *Fecalibacterium prausnitzii* decrease, while the proportions of *E. coli*, Proteobacteria, and Staphylococcus increase [29]. Additionally, the microbiotas of elderly individuals can have greater variability or be imbalanced among different bacterial species. Moreover, the microbiomes of older individuals tend to represent a pro-inflammatory phenotype based on decreased potential for vitamin B12 synthesis, increased potential for DNA damage, stress response, and immune system deterioration [28-29].

Genetic Structure

Increasing evidence suggests that the host's genetics can influence and interact with the gut microbiota. It has been observed that family members have more similar microbiotas than non-relatives, raising the possibility that genetics can shape the microbiome [30]. In a study examining fecal samples from 977 individuals, including monozygotic and dizygotic twin pairs, it was shown that twins had more similar microbiotas than non-twins, and monozygotic twins had more similar microbiotas than dizygotic twins. Furthermore, the *Christensenellaceae* family was seen as the most heritable taxon and was associated with a lower body mass index [29-30].

Lifestyle

The idea that regular exercise and increased physical activity support the maintenance of the gut microbiota has recently attracted researchers' interest. Increased physical activity provides effective treatment and preventive strategies for many chronic diseases associated with the microbiota [27]. It has been found that an active lifestyle increases the diversity of the gut microbiota compared to a sedentary lifestyle. Active lifestyle behaviors used as therapeutic strategies against obesity and type 2 diabetes improve various metabolic and inflammatory parameters in chronic diseases. Among inactive individuals and competitive athletes, athletes' microbiotas have reported higher alpha diversity associated with dietary patterns and protein consumption. In active women, a significant abundance of *Lachnospiraceae*, *Akkermansiaceae*, and *Faecalibacterium* bacteria has been observed, along with a lower abundance in the *Bacteroidetes* phylum [25-27]. In a study by Cerda and colleagues, the gut microbiota profiles of women with active and sedentary lifestyles were examined. Researchers found that continuous low-level physical exercise (up to 3 hours per week) modulated the gut microbiota and could increase the richness of bacteria supporting health (2). It is thought that physical exercise enhances microbial diversity and increases the population of health-beneficial bacteria. Modifying diet and exercise habits to regulate the gut flora population can be a powerful tool in preventing or treating many future diseases.

Geographic Location

The gut microbiota varies based on geographic location due to various microbial and environmental pressures, which can change the diversity and abundance of local bacterial species. The microbiota during seasons with scarce food differs from that in seasons with abundant food. In rainy seasons with high consumption of fruits and fiber-rich foods, *Bacteroides* (especially *Prevotella*) are abundant, while in dry and hunting seasons, they are less [26]. Different ethnic geographic communities have distinct genetic backgrounds, regional diets, and cultural practices. Certainly, regions with abundant resources have easier access to better sanitation and health services compared to developing countries. Thus, when designing studies to assess geographical variations in gut microbiota, there are trends attributable to many differences besides geographic separation. Nevertheless, comparisons between several developed and developing regions have provided some enlightening information that geographic-related variables are among the strongest drivers of microbial diversity.

In a study by Filippo and colleagues aimed at examining the influence of the environment on human microbiota, the microbiotas of children living in urban areas in Italy were compared with those of children living in rural areas in Africa. It was found that the bacterial richness and diversity in the microbiotas of children living in rural Africa, who were fed a fiber-rich and plant-based diet, were higher than those in the microbiotas of Italian children fed an animal-based diet. Italian children's gut microbiotas had higher amounts of *Firmicutes* and *Proteobacteria*, while African children had more *Prevotella*, *Xylanibacter*, and *Treponema*. Additionally, it was observed that African children's feces had less short-chain free fatty acids compared to Italian children [27-28]. In their study investigating enterotypes of the human gut microbiome, Arumugam and colleagues made a comparison between different continental populations and reported that different community structures

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emerged, driven by the composition of the *Bacteroidetes* phylum [29).

In their research, Dominguez and colleagues examined the relationship between living location and the cancer-microbiota connection. They compared the gut microbiotas of adult African Americans, who have a high risk of colon cancer, with those of rural indigenous Africans, who have a low risk. It was found that the feces of rural indigenous Africans were dominated by total bacteria, butyrate-producing bacteria, and *Prevotella*; whereas the microbiotas of African Americans were dominated by *Bacteroides*. Additionally, researchers reported that indigenous Africans had higher concentrations of short-chain fatty acids, while African Americans had higher fecal secondary bile acid concentrations (30).

In Danish, Spanish, Italian, French, Japanese, and American adults, the dominant genera in the phylum were marked by *Prevotella* or *Bacteroides*, or a less distinct *Ruminococcus*. Surprisingly, it was shown that children do not develop a microbial community marker of *Bacteroides* or *Prevotella* until they are weaned [31]. In a large-scale study involving individuals from urban areas in the USA and rural villages in Venezuela and Malawi, Yatsunenko and colleagues examined how gut microbiomes differ across human populations based on age and geography. They reported that *Prevotella* dominated the microbiotas in Malawi and Venezuela, while *Bacteroides* dominated in North American samples. Comparing samples from the USA with those from Venezuela and Malawi, there was much less difference between the two rural microbiotas. The taxa separating the two rural communities were more common in Venezuelan babies and were distinguished by different distributions of the *Clostridia* class and predominantly *Enterococci* within the *Firmicutes* phylum. Additionally, metagenomic analysis revealed enrichment in the glycan and urease metabolic pathways in Venezuelan and Malawian babies, indicating an increased ability to harvest nitrogen and glycans from breast milk as an energy source. This enhanced metabolic activity in the microbiotas of Venezuelan and Malawian babies could be an adaptation to the decreasing volume of nutrition available to these babies compared to North Americans [32]. The *Prevotella-Bacteroides* distinction was also observed when comparing children living in a slum in Bangladesh with affluent American children. In the study by Lin and colleagues examining distinct distal gut microbiome diversity and composition in healthy children from Bangladesh and the USA, it was found that Bangladeshi and American children had different fecal bacterial community membership and structure. The microbiota of Bangladeshi children, although similar to Bangladeshi adults, had a lower ratio of *Bacteroides* and richness in *Prevotella*, *Butyrivibrio*, and *Oscillospira* compared to American children [33].

Antibiotic Use

Antibiotics are widely used to prevent or treat bacterial infections in humans and animals, and also as growth-promoting additives in animal feeds. Exposure to antibiotics can occur in two different ways. The first is through short-term high-dose exposure to antibiotics via clinical use or self-medication; the other is through long-term low-dose exposure to antibiotics from contaminated food or drinking water. The recent increase in antibiotic consumption has become a global concern. In a study examining community antibiotic consumption measured in DDD (Defined Daily Dose)/1000 people/day, it was reported that while community antibiotic consumption was 18.71 in 2004, it significantly increased to 31.26 in 2016. Concerns about the adverse effects of widespread antibiotic use on the human gut microbiota have also significantly increased. Studies have reported that the gut microbiota is involved in host metabolism, pathogen resistance, immunomodulation, and even neural functions. Therefore, the balance of the gut microbiota is extremely important for the host's health. Disorders in the gut microbiota due to antibiotics will definitely lead to undesirable outcomes in the host. Unconscious antibiotic consumption is another significant factor altering microbiota content. Antibiotics can have short and long-term effects on the gut microbiota, with reductions in abundance and diversity observed within 3-4 days after antibiotic intake [34]. In a study by Jernberg and colleagues investigating the long-term ecological effects of antibiotic intake on the human gut microbiota, researchers examined fecal samples from individuals exposed to clindamycin and a control group over a 2-year study period. The study reported a sharp decline in the clonal diversity of *Bacteroides* isolates and the long-term persistence of highly resistant clones as a direct response to antibiotic exposure. Researchers also showed that this decrease in *Bacteroides* diversity could continue for up to 2 years after antibiotic intake [35]. In a study by Panda and colleagues evaluating the short-term effect of antibiotics on the human gut microbiota, the microbiotas of 21 patients receiving broad-spectrum antibiotics like fluoroquinolones and β-lactams were evaluated before and after treatment. The study found that fluoroquinolones and β-lactams significantly reduced microbial diversity by 25% and reduced the core phylogenetic microbiota from 29 to 12 taxa. At the phylum level, these antibiotics increased the *Bacteroidetes/Firmicutes* ratio and increased the proportion of unknown taxa in the *Bacteroides* genus [36]. Another significant issue arising from frequent antibiotic use is antibiotic-associated diarrhea. While 5 to 29% of those taking antibiotics develop antibiotic-associated diarrhea, in a third of these cases, the cause is *Clostridium difficile (C. difficile)*. A reduction in diversity has been shown in the microbiotas of patients with *C. difficile* infection [37].

This comprehensive exploration provides valuable insights into the multifaceted influences shaping the gut microbiota, highlighting the interconnected roles of diet, lifestyle, genetics, geography, and antibiotic use. Each factor contributes uniquely to the overall microbial ecosystem, underscoring the complexity of the human microbiome and its profound implications for health and disease.

Medications: Impact on Microbiota

The use of medications can also lead to changes in the microbiota. Proton pump inhibitors (PPIs), prokinetic agents, laxatives, opioids, and non-steroidal anti-inflammatory drugs (NSAIDs) can cause significant damage to the microbiota. PPIs, which target bacteria and proton pumps directly, suppress stomach acid and increase stomach pH. The use of PPIs leads to the suppression of gastric flora and an increase in pathogenic bacteria. Observational studies have shown that the use of PPIs is associated with an increased risk of intestinal infections caused by *C. difficile*, *Salmonella* spp., *Shigella* spp., and *Campylobacter* spp. [2, 11]. In a meta-analysis by Lo and Chan, which examined data from 11 studies and 3,134 patients, a statistically positive relationship was found between the use of PPIs and excessive bacterial growth in the small intestine. The researchers suggested that PPI use could exacerbate the severity of NSAID-induced enteropathy. Additionally, they reported that the combined use of PPIs and NSAIDs was associated with a lower risk of gastrointestinal bleeding [27].

Prebiotic Use: Impact on Microbiota

Prebiotics are indigestible food ingredients or chemicals that selectively stimulate the growth of one or more types of microorganisms in the gut. Prebiotics support the growth of many beneficial microorganisms, increasing microbial diversity and improving inflammation [9-11]. The beneficial effects of prebiotics

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on immunological and metabolic processes in the intestines include increasing the production of short-chain fatty acids, improving intestinal integrity, aiding mineral absorption, lowering glucose levels and body weight, enhancing immunity, and having positive effects on cardiovascular system, metabolic, and inflammatory markers [27].

Fructooligosaccharides (FOS), galactooligosaccharides, and inulin are among the most well-known prebiotics. Natural sources of prebiotics include artichokes, apples, bananas, strawberries, asparagus, chicory, Jerusalem artichoke, soybeans, leeks, walnuts, almonds, barley, wheat, and flaxseed [38].

In individuals who underwent prebiotic treatment for two weeks, improvements in gut microbiota fermentation, a reduction in hunger sensation, and regulation of reactive hypoglycemia were reported. The consumption of FOS and galactooligosaccharides increases the ratio of *Bifidobacter* and *Lactobacillus* in the microbiota [2]. It has been reported that in newborns fed with formula containing FOS/galactooligosaccharides, there is an increase in *Bifidobacter*, secretory IgA, while pathogenic microorganisms, fecal pH, rates of atopic diseases, infections decrease, and regular bowel habits improve. The consumption of prebiotics can restore gut microbiota function and diversity to its original state [39].

Probiotic Use: Impact on Microbiota

Probiotics are live microorganisms that, when consumed in adequate amounts, strengthen the characteristics of the gut flora and have a positive effect on human health and physiology [40]. Probiotics provide benefits to the organism in metabolic processes through their antimicrobial, anti-inflammatory, antitoxigenic properties, and their effects on the modulation of the microbiota and immune system [41]. They prevent acidification of the gut by competing with pathogenic microorganisms, produce bioactive molecules, and provide immune modulation [39]. Probiotic-rich foods include breast milk, fermented milk products, and ready-made bioactive products containing species-specific bacteria [40]. *Lactobacillus spp.*, *Bifidobacterium spp.*, *Streptococcus salivarius*, *S. thermophilus*, *Enterococcus faecium* (*E. faecium*), *Escherichia coli* (*E. coli*), *Clostridium butyricum*, and *Saccharomyces boulardii* are some of the probiotics consumed for these purposes [37].

Probiotics are known to have positive effects on a variety of diseases by causing changes in the gut bacterial composition, such as in the treatment of gastrointestinal system diseases (Crohn's disease, ulcerative colitis, irritable bowel syndrome, etc.), and obesity. Numerous studies have indicated that regular consumption of probiotics increases both the total number of bacteria and the species of *Bifidobacteria* and *Lactobacilli* [32].

This comprehensive exploration underlines the diverse influences shaping the gut microbiota, emphasizing the significant roles played by medications, prebiotics, and probiotics. Each factor contributes uniquely, demonstrating the intricate connections between our lifestyle choices, medical treatments, and the complex ecosystem within our gut, all of which have profound implications for health and well-being.

Placental Microbiome

During pregnancy, the development of the placenta is particularly notable, as this highly specialized organ prevents the mother's immunogenicity against the fetus and anatomically separates the fetus and mother, affecting all organs and systems of the mother's body. This complex organ facilitates the materno-fetal exchange of molecules, including those originating from the maternal microbiota. Recently, the possible existence of a placental microbiome has become a subject of interest for researchers [36].

The development of the microbiota begins long before the baby is born. Contrary to previous belief, amniotic fluid is not sterile [42]. Studies on the microbial community of the placenta have shown the presence of bacteria during term and preterm births [3, 7]. Moreover, bacteria have been isolated from umbilical cord blood, meconium, and amniotic fluid. In some cases, the presence of bacteria in amniotic fluid is associated with disease conditions. *Mycoplasma* and *Ureaplasma* in amniotic fluid are common health problems associated with chorioamnionitis, preterm birth, and necrotizing enterocolitis (NEC) [43]. Additionally, women with vaginal infections have a much higher risk of preterm birth. Frequently, bacteria are also detected in the amniotic fluid and placentas of full-term healthy babies. Other phyla detected in amniotic fluid and placenta overlap with those commonly found in the oral microbiota, including Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, and Fusobacteria [36]. Furthermore, in mouse experimental studies, genetically marked *E. faecium* administered orally to pregnant mice was later isolated from amniotic fluid and meconium cultures [44]. Subsequent studies have aimed to demonstrate the existence of a placental microbiome.

Along with these studies, in 2014, Aagaard and colleagues performed 16S sequencing on human placenta samples, detecting a microbial community, which reignited the debate on this topic [31]. Harvey J Kliman pointed out that the detection of DNA alone does not provide evidence of the presence of living microbes [23]. Over time, issues like contamination and the inherent microbiome of testing kits (pseudo-kitome) have become significant challenges in searching for a microbiota in the placenta [24, 45]. Researchers have taken careful measures in each step of the process, including controlling for contamination during birth by including tissue samples from CS births, combining high-throughput DNA sequencing with qPCR and bacterial culture, comparing bacterial taxa found in the immediate environment (e.g., the processing room for the samples), and excluding taxa overlapping with the kitome. Even after taking these precautions, researchers were unable to detect a placental microbiome [46]. Despite these studies and challenges, a recent article reported the detection of bacterial DNA and live bacteria in the fetal intestine using 16S rRNA gene sequencing, qPCR, electron microscopy, and bacterial culture [27]. Therefore, the existence of a microbiome in the placenta remains a controversial topic.

Metabolites originating from commensal bacteria are transported via the placenta. The maternal gut microbiota plays a significant role in this maternofetal molecular transfer, modulating fetal development [8]. An important point of interest is that a healthy pregnancy leads to changes in the microbiota composition, similar to a dysbiotic assembly. However, these adaptations are physiological in the context of pregnancy, which has unique needs and requirements [1-7]. For example, the abundance of *Faecalibacterium*, a producer of SCFAs, significantly decreases in the last three months of pregnancy. This reduction in *Faecalibacterium* is also observed in populations with metabolic syndrome. Generally, pregnancy is associated with a decrease in microbial diversity and richness, a general increase in Proteobacteria and Actinobacteria, and an increase in bacterial load. The changes in the microbiota of pregnant women are attributed to adjustments in dietary habits, accompanied by changes in the pool of bacterial metabolites to fully support the development of the fetal immune system. A diet rich in fiber during pregnancy likely protects offspring against the onset of asthma through the inhibition of histone deacetylase 9 (HDAC9), mediated

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by acetate, leading to higher gene transcription of Foxp3 in Tregs. This further reduces the frequency of eosinophils and macrophages in the blood and bronchoalveolar lavage fluid and lowers serum IgE levels in infants [33].

Neonatal Microbiota

Although it is generally thought that the development of the microbiota begins at birth, studies have also detected the presence of microorganisms in structures like the placenta. Bacteria have been reported to grow in meconium samples collected within the first 2 hours after birth from newborns delivered by CS or VD, suggesting that the fetus may not be sterile [46]. In another study, amniotic fluid, placenta, colostrum, meconium, and maternal-infant fecal samples were collected from mothers and newborns who had term births by CS. The microbiota analysis using culture, PCR (polymerase chain reaction), and rRNA sequencing showed similarities between the microbiota found in the placenta, amniotic fluid, and newborn meconium, suggesting that the colonization process of the gut microbiota starts before birth [8].

It is thought that microorganisms can be transferred vertically from the mother to the fetus via the bloodstream, through the vagina and/or urinary tract, via intercellular permeability, and/or through dendritic cell transport [47]. The gut microbiome of the newborn completes its development within the first 1000 days of life. During this period, various factors change and influence the microbiota. Factors such as the mode of birth, exposure to antibiotics during pregnancy or infancy, the mother's diet, breastfeeding or formula feeding, and the transition to solid food are known to influence the microbiota in the first days of life, with the host genetic background estimated to account for only about 9% of the gut microbiota (48). High levels of Bifidobacteria in the neonatal microbiota are a fundamental component, although the microbiota has low bacterial diversity, unstable, and dynamic characteristics. Eighty subspecies of Bifidobacteria, belonging to the Actinobacteria phylum, have been identified. Subspecies of Bifidobacteria specifically identified in human gut microbiota profiles include *Bifidobacterium bifidum* (B. bifidum), *Bifidobacterium longum* (B. longum), and *Bifidobacterium breve* (B. breve), and are predominantly found in the gut microbiota of breastfed newborns [50-51]. Alongside Bifidobacteria, other frequently observed species include *Streptococcus*, *Veillonella*, *Escherichia*, *Citrobacter*, *Bacteroides*, and *Clostridia* [51].

The diversity of the gut microbiota increases in direct proportion to the infant's growth week. Up to the age of three, a child's microbiome, with a lower diversity index and higher inter-individual variability in operational taxonomic units (OTUs) compared to adults, can be distinctly distinguished from an adult microbiome [18]. The intestines of infants undergo significant developmental stages, completely dependent on the colonization of microorganisms from birth. The direct feeding from the mother's skin, the continuous mouthing of hands, feet, and other objects, especially during crawling and early walking stages when hands contact floor surfaces, encourages significant exposure to microorganisms. Additionally, children are more susceptible to infectious diseases than adults. Surprisingly, in children under three, the microbiota is largely fluctuating and more susceptible to environmental factors compared to adult microbiota [27]. Modern lifestyle changes, including improved environment, CS birth, antibiotic use, and immunization, are some of the factors that could alter the microbiota and are being studied as potential driving forces behind the sudden increase in immune-related diseases in the developed world. It has been hypothesized that there is a "critical window" early in life when the microbiota can be disrupted in a way that supports the development of diseases in later life [27]. It has been shown in an asthma animal model that antibiotic treatment during the perinatal period leads to a more severe disease phenotype [41].

This detailed examination of the factors influencing neonatal and placental microbiota underscores the intricate relationships between maternal health, environmental exposures, and the developing microbial ecosystem in the newborn, all of which play a crucial role in shaping early-life immunity and metabolic programming.

Placental Microbiome

During pregnancy, the development of the placenta is particularly notable, as this highly specialized organ prevents the mother's immunogenicity against the fetus and anatomically separates the fetus and mother, affecting all organs and systems of the mother's body. This complex organ facilitates the materno-fetal exchange of molecules, including those originating from the maternal microbiota. Recently, the possible existence of a placental microbiome has become a subject of interest for researchers [52].

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This detailed examination of the factors influencing neonatal and placental microbiota underscores the intricate relationships between maternal health, environmental exposures, and the developing microbial ecosystem in the newborn, all of which play a crucial role in shaping early-life immunity and metabolic programming.

Antibiotic Exposure and the Microbiota

Impact of Antibiotics on Microbiota

In the Western world, broad-spectrum antibiotics are commonly prescribed to infants with the aim of protecting them from diseases [19]. Excessive use of antibiotics can lead to antibiotic resistance in infancy, significantly disrupt the overall ecology of the gut microbiota, alter the abundance of established intestinal bacteria, and potentially predispose the child to certain diseases [7].

While the gut microbiota is quite resilient against disruptive factors like antibiotics, the ecology of this dense microbial population can undergo significant changes if exposed to antibiotics during very early development or over a long period [20]. This ecological disruption, combined with decreased microbial diversity in the infant gut, can create opportunities for enteric pathogens [21]. *C. difficile*, a common infection associated with antibiotic-disrupted gut microbiota, is one such example [199]. In a study by Rousseau et al., involving 53 infants aged 0 to 13 months, the onset of *C. difficile* infections in infancy was linked to changes in the gut microbiota [21]. Early life antibiotic use can also significantly affect the growth of the dominant bacterial phyla in the human gut. One study showed that infants exposed to ampicillin and gentamicin shortly after birth tended to harbor higher rates of *Proteobacteria*, *Actinobacteria*, and *Lactobacillus* up to four weeks after treatment ended compared to unexposed children [2-3].

Early life exposure to antibiotics can make infants more susceptible to a number of diseases later in life [15]. Russell et al. demonstrated that early-life treatment of mice with ovalbumin (OVA)-vancomycin altered the relative prevalence of microbial populations in the gut microbiota and, as a result, increased the susceptibility of these mice to asthma [20]. Vrieze and colleagues explored the effects of oral vancomycin on the gut microbiota, bile acid metabolism, and insulin sensitivity, finding that oral vancomycin treatment significantly affected the host physiology by reducing gut microbiota diversity,

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bile acid dehydroxylation, and peripheral insulin sensitivity in patients with metabolic syndrome. These data also indicated that the gut microbiota, especially the Firmicutes phylum, contributes to bile acid and glucose metabolism in humans [23]. Cho et al. administered subtherapeutic antibiotic treatment to young mice to create an obesity model and evaluated changes in the composition and activities of the gut microbiome. They reported that antibiotic treatment in early life altered the relative abundance of bacterial populations in the gut and changed the regulation of lipid and cholesterol metabolism, increasing colonic short-chain fatty acid levels and fat accumulation in these mice [19]. Publications also exist on the role of antibiotics in the development of irritable bowel disease (IBD) in children [25]. Shaw et al., in their study investigating whether early antibiotic use is associated with the development of IBD in childhood, reported that infants who used antibiotics in the first year of life were more likely to be diagnosed with IBD in later life [26].

Perinatal Antibiotic Exposure and Microbiota

The colonization of the neonatal gut is influenced by various perinatal factors such as the mode of birth, type of feeding, gestational age, and neonatal drug use (especially antibiotics) [15]. It is also believed that antibiotics used by the mother can affect this neonatal colonization process [16]. Considering that antibiotics are the most commonly prescribed drugs during pregnancy and are also considered environmental pollutants recently, the adverse effects of antibiotic exposure on fetal growth, development, and microbiota are increasingly attracting attention [28]. The disruption of this colonization process due to early infancy antibiotic exposure has been associated with a range of diseases and conditions in later life, including bronchopulmonary dysplasia, obesity, early wheezing, asthma, eczema, inflammatory bowel disease, and increased antibiotic resistance [27]. The most severe early complication associated with intrapartum antibiotic use is an increase in the rates of Gram-negative early-onset sepsis [13].

Studies have shown that antibiotic use in the third trimester of pregnancy is associated with higher birth weight [21]. Mueller et al. found that antibiotic use in the middle of pregnancy was associated with lower birth weight relative to gestational age, while antibiotic consumption in the third trimester was associated with higher cord blood leptin levels (a marker of fetal fat accumulation) [22]. Additionally, some clinical experimental studies have reported that antibiotic treatment during pregnancy increases the fetus's birth weight [25]. These study results indicate that antibiotic use during pregnancy affects fetal growth and development and is associated with neonatal birth outcomes.

Antibiotics are commonly used in the perinatal period to treat urinary and bacterial vaginosis and, in the intrapartum/peripartum period, as a preventive measure to reduce infection risk in the mother and newborn [28]. Most antibiotics prescribed to mothers are Beta-Lactams (typically ampicillin or penicillin) applied according to guidelines aimed at preventing neonatal Group B Streptococcus (GBS) infection and antibiotics used to prevent maternal morbidity after CS birth [29]. Guidelines for the prevention of GBS infection and the practice of surgical antimicrobial prophylaxis during CS birth have been updated recently, leading to an increase in the use of prophylactic antibiotics during birth and consequently in the antibiotic exposure of the infant [23]. Currently, 20-25% of pregnant women are prescribed antibiotics, and antibiotics constitute 80% of all drugs prescribed to pregnant women [33]. As a result, newborns have a high likelihood of being exposed to antibiotics.

Prophylactic antibiotics given before surgical incision during CS birth cross the placenta and expose the fetus to antibiotics at a time when the human gut is being colonized by microbes. The mode of birth is known to influence the composition of the gut microbiota during the neonatal period and infancy. Moreover, the baby's gut microbiota plays a role in the development of the immune system, including the regulation of responses to antigens and inflammation. While the effect on the gut microbiota in children born via CS is less pronounced, intrapartum antibiotics alter the gut microbiota of infants [34]. Perinatal and early-life antibiotic exposure has been linked to an increased risk of obesity in studies. Newborns delivered by CS are associated with a higher risk of obesity, and it is unclear how much of this association is explained by perinatal antibiotics given during birth. It is hypothesized that early exposure to antibiotics predisposes the host to an obesity-prone metabolic phenotype due to harmful disruptions in the gut microbiota that continue even after antibiotics are discontinued. Murine models support this hypothesis, suggesting a causal role for antibiotic-modified microbiota in development [8, 9]. CS birth has a long-term effect on the gut microbiome, but studies on the effects of perinatal and postnatal antibiotics on the neonatal gut microbiome, breast milk microbiota, and the child's later obesity risk are limited. Identifying modifiable risk factors in the perinatal period can provide enlightening recommendations for preventing obesity and complications in later life stages.

CONCLUSION

This study has highlighted the complex interplay between prophylactic antibiotics administered during cesarean sections and the long-term health outcomes of neonates. It is evident that these antibiotics, which permeate the placenta before the surgical incision, expose the fetus to significant microbial influences at a critical time when the human gut is undergoing initial colonization. This exposure can fundamentally alter the composition of the newborn’s gut microbiota, which plays a crucial role in the early development of the immune system by modulating responses to antigens and inflammation.

Prophylactic antibiotics given before the surgical incision during cesarean section (CS) permeate the placenta, subjecting the fetus to antibiotics when the human gut is colonized by microbes. It's known that the mode of birth affects the composition of the newborn's gut microbiota during both the neonatal and infant stages. Additionally, the baby's gut microbiota plays a role in developing the immune system by regulating responses to antigens and inflammation. Although the impact on gut microbiota is less pronounced in CS-born children, antibiotics administered during labor alter the infants' gut microbiota (34). Early life exposure to antibiotics, including the prenatal and perinatal periods, has been associated with an increased risk of obesity. Newborns delivered by CS are linked with a higher risk of obesity, but the extent to which this association is due to perinatal antibiotics given during birth remains unclear. Early exposure to antibiotics is believed to predispose the host to an obesity-prone metabolic phenotype through harmful disruptions in gut microbiota that persist even after discontinuing the antibiotics. Murine models support this hypothesis, suggesting a causal role for antibiotic-altered microbiota in development. CS birth has a long-term effect on the gut microbiome, yet studies on the impact of antibiotics used during the perinatal and postnatal periods on the neonatal gut microbiome, breast milk microbiota, and the child's future obesity risk are limited. Identifying modifiable risk factors during the perinatal period can provide insightful guidance for preventing obesity and its complications in later life stages.

Antibiotics used during childbirth in pregnant women are typically

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administered according to guidelines as prophylactic antibiotics or more often before the onset of labor as non-prophylactic. These antibiotics can affect the early microbial colonization of the newborn in two primary ways. First, the antibiotics taken by the mother pass into the newborn's bloodstream via the umbilical cord and remain for at least ten hours after administration, likely affecting early colonization [35]. Second, the antibiotics ingested by the mother alter the mother's vaginal and gut microbiome, subsequently impacting the vertical microbial transmission process and postnatal infant immunity [27, 28]. The presence of antibiotic residues in breast milk has been shown in studies [29, 40], leading to exposure of breastfed infants to antibiotics throughout the breastfeeding process. Additionally, the use of antibiotics is inevitable in the neonatal period as newborns are vulnerable to bacterial infections.

There is a significant reduction in the incidence of perinatal infection attributed to prophylactic antibiotic administration [41]. However, concerns exist regarding the adverse health effects of administering antibiotics to mothers and their newborns, including increased risk of resistant bacterial infections, allergic reactions, and disruption of the normal microbiota, which can lead to short- or long-term health outcomes. Disruptions in gut microbiota due to antibiotic treatments often result in altered colonization by various gut pathogens [42]. In a study evaluating the effect of intrapartum antibiotic prophylaxis on early neonatal gut composition and the anti-Streptococcus activity of Bifidobacterium strains, researchers noted a significant decrease in Bifidobacterium numbers in infant feces following maternal antibiotic treatment compared to those born to untreated women [43].

In a controlled study by Tapiainen et al. involving 149 newborns delivered vaginally and sampled within the first 24 hours, researchers compared the effects of intrapartum antibiotic prophylaxis (IAP), postnatal antibiotics, or their combinations on gut microbiome and the emergence of antimicrobial resistance. They found that gut colonization in newborns differed in both the IAP and postnatal antibiotic groups compared to the control group, with these differences persisting at six months and not being mitigated by lactobacillus consumption [44]. There are limited studies on the impact of prenatal prophylactic antibiotic use on the neonatal microbiota [44, 45]. In a pharmacokinetic study related to prophylactic cefazolin, it was reported that the therapeutic dose of cefazolin administered 1 hour before CS delivery was maintained in the newborn for at least 6 hours [46]. Experimental studies have shown that even a single dose of antibiotics at therapeutic levels can change the microbiome structure during the critical window before weaning, leading to predisposition to inflammatory bowel disease, obesity, and other metabolic diseases in the long term [47-50].

Conflict of interest

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