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Exploring the Impact of Prophylactic Antibiotics During Cesarean Delivery on Neonatal Microbiota: A Comprehensive Review Article

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Abstract

The use of prophylactic antibiotics during cesarean sections (CS) significantly impacts neonatal health by influencing the early colonization of the gut microbiota. Administered before surgical incision, these antibiotics cross the placenta, exposing the fetus to microbial disruptions at a critical stage of immune system development. This study examines the effects of perinatal antibiotic exposure on neonatal gut microbiota composition and its long-term health implications. Findings indicate that antibiotics disrupt microbial diversity, reduce beneficial bacteria like Bifidobacterium, and promote colonization by opportunistic pathogens. Such alterations have been linked to increased risks of obesity, inflammatory bowel disease, and metabolic disorders later in life. Maternal antibiotic use also affects vertical microbial transmission, altering the maternal vaginal and gut microbiota and exposing newborns to antibiotic residues through breast milk. While prophylactic antibiotics effectively reduce perinatal infections, their widespread use raises concerns about antibiotic resistance and long-term health consequences. Experimental studies show that even a single dose during critical developmental windows can predispose neonates to chronic diseases. This study highlights the need for careful evaluation of antibiotic use during the perinatal period to minimize adverse effects on neonatal microbiota and optimize long-term health outcomes. Identifying modifiable risk factors and refining clinical guidelines are essential steps toward balancing the benefits of infection prevention with the risks of microbiota disruption.

Key Words: Prophylactic Antibiotics, Cesarean Section, Neonatal Microbiota, Microbial Diversity

Sezaryen Doğumlarda Kullanılan Profilaktik Antibiyotiklerin Yenidoğan Mikrobiyotası Üzerindeki Uzun Vadeli Etkileri: İnceleme Makalesi

Özet

Sezaryen doğumlarda (CS) kullanılan profilaktik antibiyotikler, yenidoğan sağlığı üzerinde önemli etkiler yaratarak bağırsak mikrobiyotasının erken kolonizasyonunu etkilemektedir. Cerrahi kesiden önce uygulanan bu antibiyotikler plasentayı geçerek fetüsü, bağışıklık sisteminin gelişiminde kritik bir aşamada mikrobiyal bozulmalara maruz bırakmaktadır. Bu çalışma, perinatal dönemde antibiyotik maruziyetinin yenidoğan bağırsak mikrobiyotası üzerindeki etkilerini ve bunun uzun vadeli sağlık sonuçlarını incelemektedir. Bulgular, antibiyotiklerin mikrobiyal çeşitliliği bozduğunu, Bifidobacterium gibi faydalı bakterilerin azalmasına ve fırsatçı patojenlerin kolonizasyonunun artmasına yol açtığını göstermektedir. Bu tür değişimlerin, ilerleyen yaşamda obezite, inflamatuvar bağırsak hastalıkları ve metabolik bozukluklar riskini artırdığı tespit edilmiştir. Anneye uygulanan antibiyotikler ayrıca, maternal vajinal ve bağırsak mikrobiyotasını değiştirerek mikrobiyal dikey geçişi etkilemekte ve anne sütü yoluyla antibiyotik kalıntılarına maruz kalmaya neden olmaktadır. Profilaktik antibiyotikler perinatal enfeksiyonları etkili bir şekilde azalttığı halde, yaygın kullanımları antibiyotik direnci ve uzun vadeli sağlık üzerindeki olumsuz etkilerle ilgili endişelere yol açmaktadır. Deneysel çalışmalar, kritik gelişim dönemlerinde tek bir terapötik dozun bile yenidoğanlarda kronik hastalıklara yatkınlık oluşturabilecek mikrobiyota değişimlerine neden olabileceğini göstermektedir. Bu çalışma, perinatal dönemde antibiyotik kullanımının dikkatle değerlendirilmesi gerektiğini, yenidoğan mikrobiyotasına yönelik olumsuz etkilerin en aza indirilmesi ve uzun vadeli sağlık sonuçlarının optimize edilmesi için modifiye edilebilir risk faktörlerinin belirlenmesinin önemini vurgulamaktadır. Enfeksiyon önlemenin faydaları ile mikrobiyota bozulmalarının risklerini dengelemek amacıyla klinik kılavuzların yeniden gözden geçirilmesi kritik öneme sahiptir.

Anahtar kelimeler: Profilaktik Antibiyotikler, Sezaryen Doğum, Yenidoğan Mikrobiyotası, Mikrobiyal Çeşitlilik

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INTRODUCTION

Human and microbial genomes have co-evolved over millennia, forming an intricate and inseparable relationship between their metabolic and survival systems. The gut microbiota, a complex ecosystem comprising bacteria, viruses, and unicellular eukaryotes, plays a central role in this symbiosis. While the term "microbiota" refers to all microorganisms inhabiting the human body, "microbiome" encompasses their collective genomes, gene products, and metabolic activities (1,2). Humans, as superorganisms, consist of approximately 10% human cells and 90% microbial cells (1,3). Although the human genome consists of around 35,000 genes, bacterial genomes collectively contribute over two million genes, making their genetic repertoire about 150 times larger than that of humans—a concept referred to as the hologenome (4). The surface area occupied by gut bacteria spans approximately 400 m^2, and their collective weight ranges between 1.5-2 kg (5,6). The gut microbiota includes roughly 100 trillion cells (10^{14}), including bacteria, viruses, and unicellular eukaryotes (7).

Each individual's gut microbiota is unique, much like a fingerprint, consisting of both shared and individualized microbial compositions. This microbial diversity is shaped by endogenous and exogenous factors, including geographic location, genetic predisposition, mode of birth, age, lifestyle, diet, antibiotic use, and medical history. For instance, Firmicutes bacteria generally increase with age, whereas Bacteroidetes tend to decrease. Dietary habits also play a pivotal role, with high-protein and animal-fat diets influencing the abundance of Bacteroides, while carbohydrate-rich and vegetarian diets favor Prevotella. Resistant starch consumption has been associated with an increase in the Ruminococcus family. Antibiotic use, however, disrupts the microbiota, leading to transient or lasting dysbiosis depending on the antibiotic type and the stage of life during which it is administered (1,2,7).

The colonization of the gut microbiota begins at birth through bacterial transmission from the mother and surrounding environment (7). While neonatal flora was historically considered sterile, evidence now suggests the presence of microbiota in meconium, likely derived from the maternal microbiota, thereby shaping the neonatal gut even before birth (4). During delivery, the mode of birth significantly influences microbiota development. Vaginal

delivery (VD) exposes the newborn to microorganisms from the maternal genitourinary tract, whereas cesarean section (CS) primarily transfers skin flora. Research by Jakobsson et al. indicates that CS deliveries result in reduced gut microbiome diversity and lower *Bacteroidetes* abundance (11).

The long-term effects of gut microbiota colonization on health and disease are an area of growing scientific interest. The microbial composition established during infancy serves as a blueprint for lifelong health. Early interactions between commensal microorganisms and the mucosal surfaces are critical for immune system development (13). Although postnatal factors are thought to dominate microbiota development, prenatal influences are increasingly recognized as contributors to the infant microbiome (14). Perinatal factors such as delivery mode, feeding type, gestational age, and exposure to medications—particularly antibiotics—affect gut colonization, with maternal antibiotic use during pregnancy being a significant modifier (15,16).

Prophylactic antibiotics administered during CS prior to surgical incision cross the placenta, exposing the fetus to antibiotics at a crucial stage of microbiome development. Evidence suggests that newborns delivered via CS face higher risks of obesity, though the extent to which this is attributable to perinatal antibiotic exposure remains unclear. Investigating the microbiota in meconium can provide insights into how intrauterine factors influence the earliest stages of gut colonization.

This study focuses on the long-term health impacts of antibiotics administered during cesarean sections, specifically examining disruptions to the neonatal gut microbiota. By exploring how early microbial imbalances contribute to health outcomes, this research aims to uncover pathways that link early-life microbial disruptions with the development of chronic health conditions.

GENERAL INFORMATION

Microbiota

Human and microbial genomes have co-evolved, forming a symbiotic relationship that integrates their metabolic activities. The gut microbiota, consisting of archaea, bacteria, viruses, and fungi, plays a vital role in human health (17,18). While "microbiota" refers to these microorganisms collectively, "microbiome" describes their genomes (4). Humans, as superorganisms, comprise 10% human cells and 90% microbial cells, with the microbiota possessing a gene pool 150 times larger than the human genome (1). An adult’s gut microbiota includes around 10^{14} cells, weighing 1.5–2 kg,

and is now considered an "organ" with significant physiological influence (6).

The gut microbiota is most abundant in the colon, where it outnumbers human cells in the body. Its composition is influenced by factors such as diet, age, and lifestyle. Advanced molecular methods, including 16S rRNA sequencing and metagenomic analysis, have enabled a deeper understanding of the microbiota's diversity and functionality (22). Dysbiosis, an imbalance in the microbiota, is linked to conditions like obesity, diabetes, and cancer (23,24). The Firmicutes-to-Bacteroidetes ratio, often associated with diet, plays a key role in metabolic health (24).

The Human Microbiome Project, launched in 2007, has provided valuable insights into the microbiota, yet many areas remain unexplored. Continued research is essential to fully understand its implications for health and disease (1).

Formation of the Microbiota

The gut microbiota is unique to each individual, influenced by factors such as birth mode (CS or VD), diet, age, genetics, lifestyle, antibiotic use, and past illnesses (18). While early studies suggested that microbiota formation began at birth, recent evidence shows that colonization starts during the intrauterine period, with bacteria such as *Escherichia, Shigella*, and *Streptococcus* detected in meconium (8,25). These bacteria, transferred from the mother, shape the neonatal microbiota even before birth (4).

The mode of birth is one of the most influential factors in early microbiota formation. Vaginal delivery exposes newborns to the mother's vaginal microbiota, including *Lactobacillus* and *Prevotella*, whereas cesarean section leads to colonization by skin flora, such as *Streptococcus* and *Corynebacterium* (8,26). These early colonization patterns impact health throughout life, with VD-associated microbiota generally promoting higher diversity and beneficial bacterial species like *Bifidobacterium* and *Bacteroides*. In contrast, CS is associated with delayed colonization of *Bacteroidetes* and higher prevalence of *C. difficile* (15,27).

Immunological and metabolic disorders have also been linked to birth mode. Studies indicate that CS increases risks of inflammatory bowel disease, celiac disease, and obesity. For instance, Blustein et al. reported that children born via CS were 1.83 times more likely to develop obesity by age 11, especially if born to obese mothers (25,26). These findings highlight the lasting impact of birth mode on microbiota and subsequent health outcomes.

Diet

Diet significantly influences the gut microbiota. Breastfed infants typically have microbiota dominated by *Bifidobacterium* and

Lactobacillus, while formula-fed infants exhibit a higher prevalence of *Enterococcus*, *Bacteroides*, and *Clostridia* (4,7). Studies show that breastfed babies have a healthier gut microbiota composition compared to formula-fed ones, with reduced colonization of pathogens like *C. difficile* (15). In adults, fiber-rich diets promote Firmicutes species that metabolize complex carbohydrates, while animal-based diets favor bile-resistant species like *Bacteroides* (16,27). Comparative studies, such as those by Filippo et al., reveal that diets rich in plant-based foods are associated with *Prevotella* dominance, while meat-based diets correlate with higher *Bacteroides* levels (25).

Age

The gut microbiota undergoes rapid changes in early life, stabilizing around age three. Vaginally delivered infants acquire microbiota resembling the maternal vaginal flora, whereas cesarean-delivered infants are colonized by skin flora (4). Breastfeeding fosters *Bifidobacterium* dominance, which decreases with the introduction of solid foods (4-6). In aging individuals, beneficial bacteria like Bifidobacterium and *F. prausnitzii* decline, while pro-inflammatory species such as *E. coli* and *Proteobacteria* increase, contributing to age-related health challenges (28-29).

Genetic Structure

Genetics also play a role in microbiota composition. Studies on twins show that monozygotic twins share more similar microbiotas than dizygotic twins, suggesting a genetic influence. The *Christensenellaceae* family, highly heritable, is linked to lower body mass index (29-30).

Lifestyle

Physical activity enhances gut microbiota diversity and supports metabolic health. Active individuals, including athletes, exhibit higher microbial richness compared to sedentary individuals, with increased populations of beneficial bacteria like *Akkermansiaceae* and *Faecalibacterium* (25-27). Exercise also modulates gut flora, promoting bacteria linked to improved inflammatory and metabolic parameters. Combining regular exercise with dietary modifications can help prevent or manage chronic diseases (2,27).

Geographic Location

Gut microbiota composition varies significantly across geographic regions due to environmental factors, diet, and microbial pressures. Seasonal food availability also influences microbiota diversity, with fiber-rich diets during rainy seasons favoring *Bacteroides* and *Prevotella*, while dry seasons reduce their abundance (26). Differences in genetic backgrounds, regional diets, and sanitation levels further shape

microbiota profiles, making geographic factors critical in microbial diversity (27-28).

Studies comparing rural and urban populations have revealed distinct patterns. For example, African children consuming fiber-rich diets exhibit higher microbial diversity, dominated by *Prevotella*, *Xylanibacter*, and *Treponema*, compared to Italian children with animal-based diets, who have more *Firmicutes* and *Proteobacteria* (27-28). Similarly, rural indigenous Africans, with low colon cancer risk, have gut microbiotas enriched with butyrate-producing bacteria and *Prevotella*, unlike African Americans, whose microbiotas are dominated by *Bacteroides* and secondary bile acids (30).

Comparisons between rural communities in Venezuela and Malawi and urban populations in the USA highlight the dominance of *Prevotella* in rural microbiotas versus *Bacteroides* in urban samples. These variations align with dietary differences, such as higher fiber consumption in rural areas. Metagenomic analyses suggest adaptations in rural microbiotas, including enhanced glycan metabolism for energy extraction from breast milk, a potential response to limited nutrition (32).

Finally, studies comparing Bangladeshi children in slums and affluent American children show lower *Bacteroides* and richer *Prevotella* and Oscillospira in Bangladeshi children, reflecting dietary and environmental influences on microbiota composition (33).

Antibiotic Use

Antibiotics, widely used in healthcare and agriculture, significantly impact gut microbiota. Exposure can occur via short-term high doses or long-term low doses from contaminated food and water. Studies highlight the adverse effects of antibiotics on microbial diversity and balance, critical for health. For instance, clindamycin exposure reduces *Bacteroides* diversity for up to two years (35). Broad-spectrum antibiotics, like fluoroquinolones, can decrease microbial diversity by 25% and disrupt core taxa, increasing the *Bacteroidetes*/*Firmicutes* ratio (36). Antibiotic-associated diarrhea, often linked to *C. difficile*, affects 5–29% of users, further underscoring the risks of overuse (37).

Medications: Impact on Microbiota

Medications such as proton pump inhibitors (PPIs), laxatives, and NSAIDs also alter the microbiota. PPIs, by suppressing gastric acid, increase pathogenic bacteria like C. difficile and Salmonella spp. (11). Meta-analyses link PPIs to small intestine bacterial overgrowth and heightened risks of NSAID-induced enteropathy (27). Combined use of PPIs and NSAIDs, however, may reduce gastrointestinal bleeding.

Prebiotic Use: Impact on Microbiota

Prebiotics, indigestible food components, selectively promote beneficial bacteria like *Bifidobacterium* and *Lactobacillus*. Natural sources include artichokes, bananas, asparagus, and flaxseed. Prebiotic intake enhances short-chain fatty acid production, intestinal integrity, and immune function while reducing inflammation and body weight (9-11, 27). In newborns, formula containing prebiotics increases beneficial bacteria and lowers atopic disease risks (39). Regular prebiotic consumption helps restore gut microbiota balance and diversity.

Probiotic Use: Impact on Microbiota

Probiotics are live microorganisms that, when consumed adequately, enhance gut health by modulating microbiota composition, reducing pathogenic bacteria, and providing immune support. Common probiotics include *Lactobacillus spp., Bifidobacterium spp.*, and *Saccharomyces boulardii*, found in breast milk, fermented dairy products, and bioactive supplements (39,40). Regular probiotic consumption has shown benefits for gastrointestinal disorders like Crohn's disease and irritable bowel syndrome, as well as metabolic conditions such as obesity. Studies highlight increased *Bifidobacteria* and *Lactobacilli* diversity with consistent probiotic use (32).

Placental Microbiome

Recent research challenges the notion that the intrauterine environment is sterile. Studies have identified bacterial DNA in amniotic fluid, placenta, and fetal tissues, suggesting maternal gut microbiota may influence fetal development via the placenta (36,42). Commonly detected bacteria include *Firmicutes, Bacteroidetes, and Proteobacteria*, overlapping with the maternal oral microbiota. However, contamination and pseudo-kitome issues complicate the confirmation of a true placental microbiome (23,24).

Despite debates, maternal microbiota metabolites, such as SCFAs, are known to cross the placenta, shaping fetal immune development. Pregnancy-related microbiota changes, such as reduced diversity and increased Proteobacteria, are considered adaptive to support fetal growth. A fiber-rich diet during pregnancy further enhances beneficial outcomes, protecting offspring from asthma through immune modulation mechanisms like HDAC9 inhibition and Treg cell activation (1-7,33).

Neonatal Microbiota

Contrary to the belief that microbiota development begins at birth, studies suggest that colonization starts prenatally. Microorganisms have been detected in the placenta, amniotic fluid, and meconium of newborns, indicating

vertical transmission from the mother via the bloodstream, vaginal tract, or dendritic cells (46-47). The neonatal microbiota is highly dynamic, influenced by factors such as birth mode, antibiotic exposure, breastfeeding, and the transition to solid foods. While the microbiota in newborns has low diversity, it is dominated by beneficial *Bifidobacterium* species, particularly in breastfed infants, alongside *Streptococcus, Bacteroides, and Clostridia* (50-51).

By age three, the gut microbiota stabilizes, though it remains distinct from adult microbiota. Modern lifestyle factors like cesarean delivery, antibiotics, and reduced environmental exposures are linked to immune-related diseases, emphasizing the importance of the "critical window" for microbiota development in early life (27). Studies have demonstrated that early-life antibiotic use can increase the risk of diseases such as asthma, highlighting the long-term impact of neonatal microbiota disruption (41).

Placental Microbiome

Research into the placental microbiome has revealed bacterial DNA and microorganisms in amniotic fluid and placenta, challenging the notion of a sterile intrauterine environment. Commonly detected bacteria include *Firmicutes, Bacteroidetes, and Proteobacteria*, which overlap with the oral microbiota. These findings suggest maternal microbiota influences fetal development via the placenta (11,24). However, contamination and kit microbiome issues have raised debates about whether the placenta hosts a true microbiome (23-26).

During pregnancy, maternal microbiota undergoes adaptive changes, such as decreased diversity and increased *Proteobacteria*. These changes support fetal immune development by modulating bacterial metabolite pools, such as SCFAs. Fiber-rich diets during pregnancy are particularly beneficial, potentially reducing asthma risk in offspring through immune regulation mechanisms like HDAC9 inhibition and Treg activation (28-33).

ANTIBIOTIC EXPOSURE AND THE MICROBIOTA

Impact of Antibiotics on Microbiota

Broad-spectrum antibiotics are commonly used in infancy to prevent infections, but their overuse disrupts gut microbiota, reduces diversity, and may increase susceptibility to diseases like *C. difficile* infection (7,21). Early antibiotic exposure alters microbial populations, favoring *Proteobacteria, Actinobacteria,* and *Lactobacillus*, and is linked to long-term health risks such as asthma, metabolic disorders, and IBD (19,20,26). Studies in murine models also demonstrate that antibiotics disrupt microbiota-related bile acid and glucose metabolism, increasing fat accumulation and colonic SCFA levels (23).

Perinatal Antibiotic Exposure and Microbiota

Perinatal antibiotic exposure, including maternal and neonatal use, impacts gut colonization and is associated with complications like bronchopulmonary dysplasia, obesity, and increased antibiotic resistance (27). Antibiotics prescribed during pregnancy, particularly Beta-Lactams, are commonly used to prevent GBS infections and maternal morbidity during cesarean delivery (28-29). Prophylactic antibiotics cross the placenta, affecting neonatal microbiota development at a critical stage (34).

Antibiotics used in late pregnancy have been linked to increased birth weight, while those used earlier are associated with lower birth weights and changes in fetal fat accumulation (21,22). Early-life antibiotic exposure disrupts the neonatal microbiota, increasing obesity risk and influencing metabolic phenotypes (8,9). CS births, which involve higher antibiotic exposure, are particularly associated with altered gut microbiota and long-term health risks.

Identifying modifiable perinatal risk factors could help mitigate complications like obesity and immune-related disorders later in life. Addressing antibiotic use during this critical window is essential for promoting healthy microbiota development and reducing long-term health risks.

CONCLUSION

This study underscores the complex relationship between prophylactic antibiotic use during cesarean sections (CS) and neonatal health outcomes. Antibiotics administered before surgical incision cross the placenta and influence microbial colonization at a critical stage of gut development, which is vital for immune system modulation. Early disruptions in gut microbiota due to antibiotics have been linked to long-term health risks, including obesity, inflammatory bowel disease, and metabolic disorders.

Maternal antibiotic use during labor impacts neonatal microbiota through direct transfer via the umbilical cord and indirect effects on the maternal vaginal and gut microbiome, altering vertical microbial transmission. Antibiotic residues in breast milk further expose breastfed infants, compounding these effects. While prophylactic antibiotics reduce perinatal infection rates, their role in altering microbial diversity and promoting antibiotic resistance remains a concern.

Studies highlight a reduction in *Bifidobacterium* colonization and persistent microbiota alterations in infants exposed to intrapartum or postnatal antibiotics. Experimental evidence shows that even a single therapeutic dose of antibiotics during critical windows of microbiome development can predispose neonates to chronic conditions like obesity and inflammatory diseases. Identifying modifiable risk factors, such as the timing and necessity of antibiotic use during the perinatal period, offers opportunities

to mitigate these risks and promote healthier long-term outcomes.

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