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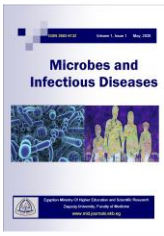

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Review article

Influence of mode of delivery on neonatal microbial colonization and susceptibility to infections

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ABSTRACT

Background: The mode of delivery significantly influences neonatal microbial colonization, with long-term implications for health and disease susceptibility. Vaginal delivery exposes neonates to maternal vaginal and intestinal microbiota, fostering a diverse and beneficial microbial environment crucial for immune development and overall health. In contrast, cesarean section (C-section) bypasses this natural exposure, leading to colonization by skin and environmental microbes, which can result in reduced microbial diversity and increased susceptibility to infections and immune-mediated disorders. This paper examines the impact of delivery methods on neonatal microbial colonization patterns and associated health outcomes. Vaginally delivered neonates acquire beneficial bacteria such as Lactobacillus and Bifidobacterium, which support gut health, immune modulation, and pathogen resistance. In contrast, C-section delivery often results in delayed colonization and an increased prevalence of hospital-acquired bacteria, potentially leading to higher risks of conditions such as asthma, allergies, and metabolic disorders. Interventions such as vaginal seeding and probiotic supplementation offer potential solutions to mitigate the microbial deficits associated with C-sections. Encouraging breastfeeding further enhances microbial diversity and immune function. Policy recommendations should focus on reducing unnecessary C-sections while promoting strategies that support neonatal microbial health. Understanding the relationship between delivery mode and neonatal microbiome development is essential for improving health outcomes. Healthcare providers should consider microbial implications when determining delivery methods to optimize neonatal health.

Introduction

The neonatal period represents one of the most crucial stages in human development, particularly in terms of microbial colonization. During this time, the infant's body becomes host to a complex community of microorganisms that play a significant role in shaping their health and immunity [1]. This microbial colonization begins at birth, with the mode of delivery being a critical determinant of the types and diversity of microbes introduced to the neonate [2]. The first few hours and days of life are pivotal for this colonization process, and any disruption during this period can have profound implications for short- and long-term health.

The mode of delivery, whether vaginal or cesarean section, exerts a strong influence on the initial microbial exposure of the neonate. Vaginal

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delivery facilitates direct contact with the maternal vaginal and intestinal microbiota, offering neonates a rich microbial environment that fosters the development of a robust and diverse microbiome [3]. This diverse microbial exposure is critical for the priming and maturation of the neonatal immune system, ensuring that the infant's body is equipped to fend off pathogens while maintaining tolerance to non-harmful microorganisms. In contrast, cesarean delivery bypasses the maternal vaginal canal, depriving the neonate of exposure to this critical microbial environment. Instead, neonates delivered via cesarean section are predominantly colonized by skin-associated microbes and environmental bacteria, including those from hospital surfaces and healthcare providers [4]. This altered microbial colonization pattern results in a less diverse microbiome, which can compromise immune development and increase susceptibility to infections [5].

The significance of these differences becomes even more apparent when considering the long-term health implications of neonatal microbial colonization. A well-balanced and diverse microbiome is not only essential for protecting against immediate infections but also plays a key role in preventing immune-mediated disorders later in life [6]. For instance, exposure to specific beneficial bacteria during vaginal delivery helps establish microbial communities that can modulate immune responses and maintain intestinal integrity. Conversely, cesarean-delivered neonates often exhibit delayed colonization and lower microbial diversity, which are linked to higher risks of developing chronic conditions such as asthma, allergies, and metabolic disorders [7].

Impact of Delivery Methods on Neonatal Microbiome Development

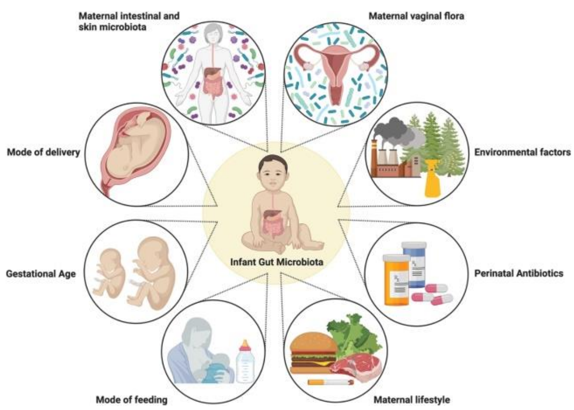
Microbial colonization in neonates begins at birth, with the mode of delivery dictating the microbial communities to which the infant is initially exposed. Vaginal delivery provides an environment that supports the transfer of maternal vaginal and intestinal microbiota to the neonate [8]. This transfer is facilitated by the direct contact that occurs during the passage through the birth canal. Neonates born vaginally are exposed to beneficial bacteria such as *Lactobacillus* and *Bifidobacterium*, which colonize the neonate's skin, respiratory tract, and gastrointestinal system. These bacteria are instrumental in the early establishment of a diverse and resilient microbiome, which serves as a foundation for optimal health and immune function [9].

The spontaneous microbial translocation during vaginal delivery is augmented by the neonate's exposure to maternal intestinal bacteria, which frequently co-occur with the vaginal microbiota after birth. The intestinal microbiota comprises several anaerobic bacteria that facilitate gut colonization and are involved in food metabolism, immunological regulation, and pathogen defense [10]. This process is essential for the formation of a healthy gut microbiota, which is vital for regulating immune responses and sustaining homeostasis.

Conversely, cesarean birth disrupts the natural mechanism of microbial transmission. Neonates born via cesarean section do not encounter the mother vaginal and intestinal microbiota during parturition. Their initial microbial colonization is influenced by environmental variables, such as exposure to the mother's skin microbiome, healthcare staff, and bacteria from hospital surfaces and equipment [9].

The predominant bacteria colonizing cesarean-delivered neonates include *Staphylococcus*, *Corynebacterium*, and *Streptococcus* species, which are commonly found on human skin. While these bacteria are not inherently harmful, the lack of exposure to vaginal and intestinal microbes limits the diversity of the neonatal microbiome, which can have adverse consequences for immune development and health [10].

Figure 1. Neonatal and infact microbiota. Adopted from: Lee-Hill [11]



One of the most significant differences between vaginally and cesarean-delivered neonates lies in the diversity of their microbiomes. Vaginally delivered neonates exhibit greater microbial diversity, which is a hallmark of a healthy microbiome. This diversity enhances the microbiome's resilience, allowing it to adapt to environmental changes and effectively combat pathogenic organisms [12]. In contrast, the microbiomes of cesarean-delivered neonates are often less diverse and dominated by skin-associated microbes, which lack the metabolic and immunological benefits provided by vaginal and intestinal bacteria. This reduced diversity can impair the neonate's ability to mount effective immune responses, leaving them more vulnerable to infections and other health challenges [13].

The mode of delivery also influences the timeline of microbial colonization. Vaginally delivered neonates experience rapid and robust colonization, with beneficial bacteria establishing themselves within hours of birth [14]. This rapid colonization is critical for the early activation of the neonatal immune system, which relies on microbial signals to differentiate between harmful and harmless organisms. Cesarean-delivered neonates, on the other hand, often experience delayed colonization, with slower establishment of gut bacteria. This delay can disrupt the delicate balance between the microbiome and the immune system, increasing the risk of dysbiosis and related health issues [15].

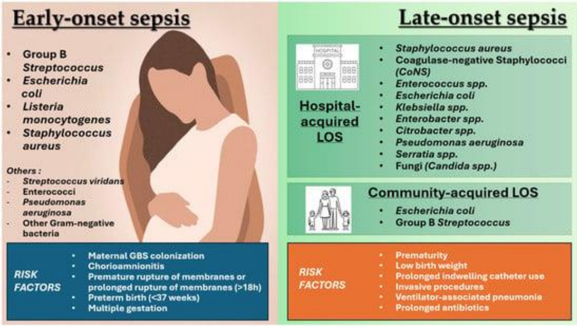
Significance for Neonatal Infection Risks

The neonatal microbiome serves as a foundational defence mechanism, playing a critical role in modulating immune responses and preventing the colonization of pathogenic microorganisms [16]. The microbes that colonize the neonate's body during the first few days of life influence the development of the innate and adaptive immune systems, shaping the infant's ability to respond to infections. Vaginal delivery, by promoting exposure to beneficial bacteria, primes the neonatal immune system and establishes a protective barrier against infections [17].

Beneficial bacteria such as *Lactobacillus* and *Bifidobacterium*, which are acquired during vaginal delivery, produce short-chain fatty acids and other metabolites that support gut health and immune function. These bacteria also compete with potential pathogens for resources, preventing harmful microorganisms from colonizing the gut. This competitive exclusion is a key mechanism by which the microbiome protects against infections, particularly in the early neonatal period when the immune system is still immature [18].

In contrast, cesarean delivery is associated with an altered and delayed microbial colonization process, which has been linked to higher rates of neonatal infections. The absence of early exposure to beneficial bacteria leaves cesarean-delivered neonates more susceptible to colonization by opportunistic pathogens, such as *Staphylococcus aureus* and *Klebsiella pneumoniae [19]*. These bacteria can cause serious infections, including neonatal sepsis and respiratory tract infections, which are major contributors to neonatal morbidity and mortality.

Figure 2. Neonatal infection and the associated risk factors. Adopted from: Rose et al[20]



The increased risk of infections in cesarean-delivered neonates is compounded by the introduction of hospital-acquired bacteria during the birth process. Cesarean deliveries often involve exposure to sterile environments and medical interventions, which can introduce bacteria that are not typically found in the maternal microbiota. These hospital-acquired bacteria may include antibiotic-resistant strains, which pose additional challenges for treatment and management [21].

Beyond the immediate risk of infections, disruptions in the neonatal microbiome due to cesarean delivery can have long-term consequences for immune development and health. The microbiome plays a critical role in educating the immune system, teaching it to distinguish between harmful and harmless microorganisms [22]. This process, known as immune tolerance, is essential for preventing excessive inflammatory responses and autoimmune disorders. Vaginal delivery facilitates this process by providing a diverse microbial environment that supports the development of regulatory T cells and other immune-modulating mechanisms [23].

Caesarean delivery, by restricting microbial diversity and postponing colonisation, undermines the immune system's capacity to acquire tolerance and sustain equilibrium. This disturbance has been associated with an elevated risk of immune-mediated diseases, including asthma, allergies, and inflammatory bowel disease. These diseases are believed to stem from the immune system's failure to adequately regulate inflammatory responses, potentially due to insufficient early microbial signals [24].

The long-term health implications of cesarean delivery underscore the importance of understanding and addressing the risks associated with altered microbial colonization. Strategies to optimize microbial transfer, such as vaginal seeding and the use of probiotics, offer promising approaches to mitigating these risks and promoting neonatal health. By prioritizing interventions that support microbial diversity and immune development, healthcare providers can help reduce the burden of infections and improve health outcomes for cesarean-delivered neonates [24].

In conclusion, the mode of delivery has a profound impact on the neonatal microbiome and its role in protecting against infections. Vaginal delivery provides a natural and effective mechanism for transferring beneficial bacteria to the neonate, supporting the establishment of a diverse and resilient microbiome. Cesarean delivery, while medically necessary in certain cases, disrupts this process and increases the risk of infections and immune-mediated disorders [22].

Microbial Colonization Patterns

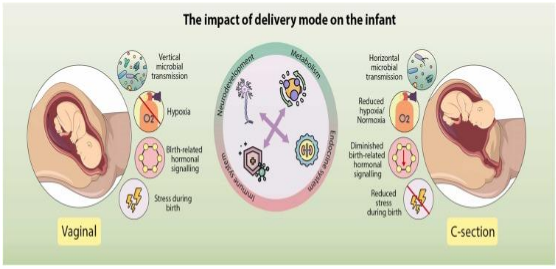
Vaginal Delivery versus Cesarean Section

The patterns of microbial colonization in neonates are profoundly shaped by the mode of delivery, with vaginal delivery and cesarean section providing distinctly different microbial exposures. During vaginal delivery, neonates are exposed to the maternal vaginal microbiota, a community rich in beneficial bacteria such as Lactobacillus species [25]. These bacteria are pivotal for initiating the colonization of the neonatal gut, creating a microbial environment that is diverse, robust, and equipped to support the neonate’s health. Lactobacillus species, in particular, play a key role in establishing an acidic gut environment that inhibits the growth of pathogenic microorganisms, thereby laying the foundation for a resilient and protective microbiome [26].

In addition to vaginal microbiota, neonates delivered vaginally also acquire gut microbiota that reflects the maternal intestinal microbiome. This dual exposure to both vaginal and intestinal bacteria significantly enhances the microbial diversity and functional resilience of the neonatal microbiome. Such diversity is vital for the activation and maturation of the neonatal immune system. The neonatal gut, colonized by these maternal microbes, serves as a dynamic interface for immune education, enabling the immune system to differentiate between beneficial and harmful microorganisms [27]. This process not only establishes a protective microbial environment but also primes the neonate’s immune defenses against potential pathogens.

In sharp contrast, neonates born through caesarean section undergo a fundamentally distinct microbial colonization process. Caesarean delivery circumvents the maternal vaginal canal, depriving neonates of exposure to the abundant microbial community found in the vaginal and intestinal microbiota. In contrast, neonates delivered via caesarean section are predominantly colonized by skin-associated bacteria, such as Staphylococcus, Corynebacterium, and Streptococcus species [29]. Skin-associated microbes predominantly influence the initial colonization in cesarean-delivered infants, resulting in a microbial community that is less diverse and functionally different from that of vaginally delivered neonates.

Figure 3. Microbial impact of delivery mode on infacts. Adopted from: Cabre, 2022 [28]



The microbial diversity in cesarean-delivered neonates is often significantly lower compared to their vaginally delivered counterparts. The decline in diversity significantly affects neonatal health, as a varied microbiome is crucial for immune system maturation and the avoidance of dysbiosis. Moreover, the aseptic surgical settings linked to cesarean delivery introduce nosocomial bacteria into the neonatal microbiome [29]. These bacteria, frequently comprising opportunistic pathogens, might inhabit the neonate's skin, respiratory tract, and gastrointestinal system, hence potentially elevating the risk of infections. The dependence on sterile conditions during cesarean sections, although essential for reducing maternal and neonatal infection risks, unintentionally disrupts the natural microbial transfer process, resulting in a microbial profile that may predispose neonates to health issues [18].

This alteration in microbial colonization patterns can have long-term health implications for cesarean-delivered neonates. The reduced diversity and delayed establishment of the neonatal microbiome associated with cesarean delivery have been linked to an increased risk of various health conditions, including allergies, asthma, obesity, and autoimmune diseases. The absence of early exposure to maternal vaginal and intestinal microbiota deprives cesarean-delivered neonates of critical microbial signals that are essential for immune system maturation and the development of a balanced gut ecosystem. Over time, this altered microbial colonization process can contribute to persistent dysbiosis, a condition characterized by an imbalance in the microbial community that negatively impacts the host's health [26].

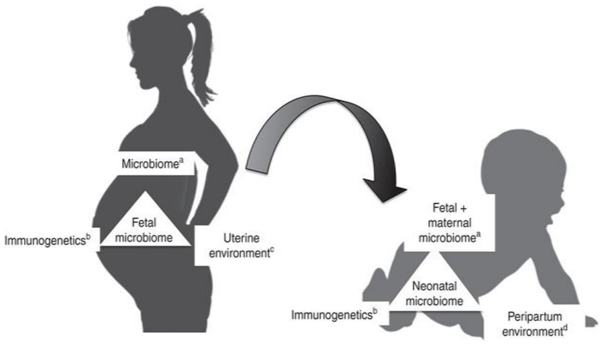
The differences in microbial colonization patterns between vaginally delivered and cesarean-delivered neonates highlight the importance of the mode of delivery in shaping the neonatal microbiome. While cesarean delivery is a life-saving intervention in many cases, its impact on microbial colonization underscores the need for strategies to mitigate these effects and optimize neonatal health outcomes. Understanding the mechanisms underlying microbial colonization in neonates and the role of the mode of delivery in this process is essential for developing targeted interventions that support the establishment of a healthy microbiome in all neonates, regardless of delivery method [25].

Role of Maternal Microbiota in Colonization

The maternal microbiota is the primary source of microbial transfer to the neonate, playing a critical role in shaping the neonatal microbiome during and immediately after birth. This process of microbial transfer is deeply influenced by the composition of the maternal microbiota, which is, in turn, affected by a variety of factors, including maternal diet, antibiotic use, health status, and lifestyle. The diversity and health of the maternal microbiota are therefore key determinants of the neonatal microbial profile and subsequent health outcomes [29].

In vaginally delivered neonates, the transfer of maternal microbiota occurs naturally and efficiently. During passage through the birth canal, neonates are exposed to a diverse microbial community that includes Lactobacillus, Bifidobacterium, and other beneficial bacteria. This exposure initiates the colonization of the neonatal gut, creating a microbial environment that is not only diverse but also tailored to support the neonate's developmental needs [30]. The maternal vaginal microbiota is uniquely suited to prepare the neonate for the transition from the sterile in utero environment to the microbe-rich external world. By providing a foundational microbial community, the maternal microbiota plays a pivotal role in establishing a resilient neonatal microbiome that supports immune system maturation and protects against infections [31].

Figure 4. Immunological signifcance of mother to child transfer. Adopted from: Romano-Keeler [32]



However, the efficiency of microbial transfer during vaginal delivery is contingent upon the health and diversity of the maternal microbiota. Factors such as antibiotic use, infections, and poor diet can disrupt the maternal microbiota, reducing its diversity and altering its composition. These changes can compromise the quality of the microbial transfer process, potentially affecting the neonatal microbiome. For instance, antibiotic use during pregnancy or delivery can diminish the abundance of beneficial bacteria in the maternal microbiota, limiting the microbial diversity available for transfer to the neonate. Similarly, maternal infections that alter the vaginal microbiota can impact the microbial exposure of vaginally delivered neonates, influencing the establishment of their microbiome [33].

Cesarean delivery disrupts the natural microbial transfer from the maternal microbiome, resulting in an altered newborn microbial profile. Neonates delivered via cesarean section lack exposure to maternal vaginal and intestinal microbiota, leading to a microbial community that inadequately represents maternal microbial health. Instead, these neonates are infected by microorganisms from the hospital environment, healthcare personnel, and maternal skin. Although these sources facilitate initial microbial colonization, they do not possess the richness and functional advantages of the maternal microbiota. The lack of maternal microbial transfer during cesarean delivery emphasizes the significance of mother microbiota health in influencing the newborn microbiome and reinforces the necessity for interventions to facilitate microbial colonization in cesarean-born infants [34,35].

The role of the maternal microbiota in neonatal colonization extends beyond the initial microbial transfer during birth. Maternal factors such as breastfeeding further influence the neonatal microbiome in the postpartum period. Breast milk contains a diverse array of beneficial bacteria, as well as prebiotics that selectively nourish the neonatal gut microbiota. For cesarean-delivered neonates, breastfeeding can partially compensate for the lack of exposure to maternal vaginal microbiota, promoting microbial diversity and resilience [34].

Neonatal Health Outcomes

Short- and Long-Term Risks of Infections

The mode of delivery has profound implications for neonatal health outcomes, particularly in terms of infection risks. In the immediate neonatal period, cesarean-delivered infants are more susceptible to infections such as neonatal sepsis and respiratory tract infections. This increased susceptibility is attributed to the delayed colonization of protective gut microbiota and the predominance of hospital-acquired bacteria. Vaginally delivered neonates, on the other hand, benefit from early exposure to beneficial bacteria, which enhance immune system activation and reduce infection risks [35].

In the long term, cesarean delivery is associated with an increased risk of developing chronic health conditions linked to dysbiosis. Altered gut microbiota in cesarean-delivered neonates has been implicated in the development of asthma, obesity, and type 1 diabetes. These conditions are thought to arise from the disruption of microbial-immune interactions during critical periods of immune development. By contrast, the diverse and balanced microbiota established through vaginal delivery provides a protective effect, reducing the risk of such chronic diseases and supporting overall health [36].

Links to Immune Development and Chronic Diseases

Both the education and regulation of the immune system are dependent on the interaction that occurs between the microbiome of the neonate and the immune system. Early exposure to microorganisms has an effect on the development of regulatory T cells, which are essential for the preservation of immunological homeostasis and the prevention of excessive inflammatory responses [37]. The creation of a complex microbial environment that supports these processes is encouraged by vaginal delivery, which in turn reduces the risk of autoimmune and allergy illnesses. The lack of early microbial exposure in neonates who were born via caesarean section hinders the development of their immune systems, which in turn increases their vulnerability to chronic inflammatory diseases. Having an understanding of these connections highlights how important it is to maximise the capacity for microbial colonization throughout the newborn period.

Influencing Factors

Antibiotic Prophylaxis During Cesarean Sections

Antibiotic prophylaxis is a standard practice during cesarean delivery to prevent maternal infections. However, this intervention significantly impacts the maternal and neonatal microbiota. Antibiotic use alters the composition of the maternal microbiota, reducing the diversity and abundance of beneficial bacteria available for transfer to the neonate [37]. Consequently, neonates exposed to antibiotics during delivery experience delayed and altered microbial colonization, which increases their risk of infections and promotes the proliferation of antibiotic-resistant bacteria. These effects highlight the need for judicious use of antibiotics during cesarean delivery and the development of strategies to mitigate their impact on neonatal microbial health.

Impact of Delayed Microbial Colonization

Delayed microbial colonization is a hallmark of cesarean delivery, with significant implications for neonatal health. The lack of maternal microbiota-derived signals at birth hinders the formation of a stable and protective microbial community. This hindrance impairs the early activation of the neonatal immune system, rendering the infant susceptible to infections and dysbiosis. Prolonged delayed colonization may disrupt the development of the gut-brain axis and lead to chronic health issues. Addressing the issue of delayed microbial colonization is essential for improving health outcomes in cesarean-delivered neonates.

Interventions to Optimize Microbial Transfer

Vaginal Seeding and Probiotics

Vaginal seeding is an emerging intervention aimed at mimicking the microbial exposure of vaginal delivery in cesarean-delivered neonates. This procedure involves swabbing the neonate with maternal vaginal fluids immediately after birth, introducing beneficial bacteria and promoting microbial diversity. Preliminary studies suggest that vaginal seeding can enhance microbial colonization and reduce the risk of infections and dysbiosis [2,3]. However, concerns about the potential transmission of pathogenic bacteria underscore the need for rigorous safety protocols and further research.

The use of probiotics is another promising strategy for optimizing microbial transfer. Probiotics containing beneficial bacterial strains such as Lactobacillus and Bifidobacterium can be administered to neonates to support gut colonization and enhance microbial diversity [38]. Evidence from clinical trials indicates that probiotics can reduce the incidence of necrotizing enterocolitis and sepsis in preterm neonates. Integrating probiotics into neonatal care protocols offers a practical and effective approach to improving microbial health in cesarean-delivered infants.

Encouraging Breastfeeding for Microbial Diversity

Breastfeeding plays a vital role in promoting microbial diversity and supporting neonatal health. Breast milk contains a rich array of prebiotics, such as human milk oligosaccharides, which selectively nourish beneficial gut bacteria. It also provides immune-modulating components that enhance microbial diversity and resilience [39,40]. For cesarean-delivered neonates, breastfeeding compensates for the lack of microbial exposure during birth, facilitating the establishment of a protective microbial community. Encouraging exclusive breastfeeding in the early neonatal period is a key strategy for optimizing microbial transfer and reducing the risk of infections and chronic diseases.

Conclusion

The mode of delivery exerts a profound influence on neonatal microbial colonization and susceptibility to infections. While vaginal delivery provides a microbial foundation critical for neonatal health, cesarean delivery poses challenges that can be mitigated through targeted interventions. Strategies such as vaginal seeding, probiotics, and breastfeeding offer practical solutions for optimizing microbial transfer and reducing the risk of infections and chronic diseases. Policymakers and healthcare providers must collaborate to balance the benefits of cesarean delivery in medically necessary cases with efforts to promote microbial health. By prioritizing maternal and neonatal care, we can ensure better health outcomes for future generations.

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