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Maternal-Neonate Microbiome: Considerations for Future Studies

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Abstract

The vital relationship between a mother's natural vaginal mucosa and an infant's healthy development is tied closely to one another. Recent studies have revealed that transferring this maternal microbiome to an infant during delivery may play a primary role in developing a child's immune system, among many other critical components of physiologic development well into adulthood. Conversely, some studies suggest that infants delivered via cesarean section who bypass this transfer of microbiota may have an increased risk of specific health deficits. Though many of these studies retain a wide range of depth, certain diseases and conditions have been identified to have higher rates of occurrence among cesarean-delivered infants, such as asthma, obesity, diabetes, allergies, ADHD, intestinal and respiratory infections, autism, dermatitis, inflammatory conditions, immune susceptibility, and more. This paper explores each of these claims through a literature review as well as proposes several considerations and indications for future studies involving the vaginal seeding of cesarean-delivered infants to compare health outcomes between infants delivered vaginally as well as cesarean alone. This qualitative study provides the opportunity for a potential change in standard clinical practice for cesarean sections, possibly shedding light on a new method of preventative medicine that has been seldom explored, which may assist in lowering the overall disease burden within populations.

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Introduction

Normal vaginal mucosa contains a vast array of bacterial, viral, and fungal species, and during the typical vaginal birthing process, these microorganisms cover the neonate in a thin film [1]. This film colonizes the epidermis and inoculates into the gastrointestinal tract via the oropharynx, thus contributing to the foundational development of the skin and gut microbiome [2]. This gut microbiome has been the center of considerable research and implicated in the development of multiple organ systems [3]. However, when patients are being delivered via Cesarean section (c-section), the customary maternal-to-infant microbiome exchange dynamic is circumvented, as the infant is no longer exposed to the maternal vagina mucosa [2]. In recent studies, the microbiome composition of neonates delivered via c-section were shown to significantly differ from their counterparts delivered vaginally [1,4]. With the steadily increasing rate of c-section deliveries, there has been a corresponding rise in the number of newborns with significantly altered microbiome compositions [5,6]. Notably, the human microbiome is known to influence multiple systemic development processes such as the immune system, the nervous system, and the functionality of numerous organs, including but not limited to the lungs, heart, skin, and the complex neuroendocrine hypothalamic-pituitary axes [7]. As a whole, it has been proven time and time again that infants delivered via c-section, compared to those delivered vaginally, have had long-lasting health effects in one regard or another, but have never showcased multiple diseases together and directly compared and contrasted these differences [8].

Inadequate infant exposure to maternal vaginal microbiota during or soon after birth may lead to an array of negative ramifications for the neonate and overall decreased quality of life

[7]. This paper will explore these contrasts in gut microbiome between the two groups of neonates and will showcase the medical and literature gap in the topic of vaginal seeding in this context.

Population: The population indicated for this study includes neonates born via live delivery each year in the United States, both vaginally and by c-section. Each year, roughly 3,650,000 live births are seen in the United States; of this number, approximately 1,170,000 were delivered via c-section [4]. Subpopulations to examine are race and sex, as both categories may present new insights into the association between neonatal gut microbiome and long-term health outcomes. Of these 1,1700,000 yearly c-sections, roughly 36.0% are black, 32.7% are Asian/Pacific islanders, 31.0% are white, and 29.0% are American Indian/Alaska natives [4].

The primary risk factor associated with this medical problem has been observed to be c-section deliveries that are not seeded with maternal vaginal mucosa. Innumerous studies showcase associations between c-section-delivered infants and long-term adverse health outcomes. An example of this association was seen in a 2019 meta-analysis of 61 observational studies that concluded c-section births are associated with autism spectrum disorders (OR:1.33, 95% CI: 1.25-1.41) and attention-deficit/hyperactivity disorders (ADHD) (OR: 1.17, CI: 1.07-1.26) [9]. Another meta-analysis comprised of 23 studies discovered a 20% increase in the risk of asthma development in children delivered via c-section as well as being found to have reduced total microbiota diversity during the first two years of life, specifically in that of Bacteroidetes phylum [10]. As autism spectrum disorders, ADHD, and asthma were discussed here, these studies will be excluded from the following section.

Literature review

A 2017 case-control study evaluated the ratio of Klebsiella:Bifidobacterium (K:B) in infants with respect to their risk of developing allergic disease [11]. The microbiomes of normal, healthy infants were found to have a low K:B ratio, whereas, in contrast, c-section-delivered infants showed a high K:B ratio at three months and were significantly more likely to develop an allergy at age 3 (OR 9.0, 95% CI: 1.46-55.5) [11]. Further on this point, some studies show neonates born via c-section have a significantly higher likelihood to develop respiratory infections such as Corynebacterium pseudodiphtheriticum, Respiratory Syncytial Virus (RSV), Streptococcus pneumonia superinfection, and more due to markedly decreased biomarkers and immune cell functions [12].

In several studies, inflammatory biomarkers such as IGF-1, MBP, NeuN, etc. were linked to the development of neural systems, the respiratory tracts, and immune system, and were found to be increased in c-section deliveries [13]. A study published in 2018 with germ-free mouse models were colonized with microbiomes associated with either low-growth or high-growth phenotypes from neonates in the NICU [13]. Microbiotas associated with low-growth phenotypes had lower levels of NeuN, neurofilament-L, MBP, IGF-1, and IGFBP3 [13]. This study suggested that the microbiota influences early neuron and oligodendrocyte development and that the effects are mainly mediated by neuroinflammatory effects and circulating IGF-1 [13]. Because of this effect, T-cell function has also been seen to differ in those delivered via c-section versus vaginal delivery [14]. For many years, it has been known that T-cell function, precisely that of Th1 cells, are decreased in neonates born by c-section [14,15]. Many indicators leave researchers to believe that the proper development of the gut microbiota is directly related to this problem these neonates experience [14,15].

A 2012 systematic review found that children, adolescents, and adults were all more likely to be obese if delivered via c-section by factors of 1.32, 1.24, and 1.5, respectively [16]. Some studies have contraindicated these findings and have found no meaningful correlation between mode of delivery and BMI in childhood or adolescence; however, given the heterogeneity of the results, some researchers have concluded that obesity is only moderately associated with c-section delivery [16].

A recent systematic review of 24 studies evaluated the mode of delivery and its impact on the prevalence of six common allergic conditions [17]. The study concluded that c-section delivered infants were more likely to develop food allergies and atopy, but had no significantly increased risk of developing eczema or atopic dermatitis [17]. A longitudinal study of 2500 children from birth-2 years of age discovered that infants born via c-section developed dermatological conditions such as atopic dermatitis at a slightly higher rate [18].

For decades, c-section delivery has been associated with increased rates of chronic inflammatory diseases such as inflammatory bowel disease, rheumatoid arthritis, celiac disease, and diabetes [19]. C-sections, in addition, are known to increase the rate of diarrhea, food sensitivities, and food allergies in children [19]. Females born by c-section had a 46% higher risk of developing type 2 diabetes, even after adjusting for BMI, as well as a higher risk of type 1 diabetes [20].

In a 2015 Danish study, it was found that children delivered via c-section had a significantly increased risk of asthma, systemic connective tissue disorders, juvenile arthritis, inflammatory bowel disease, immune deficiencies, and leukemia [19]. It was found that IgA, IgG, and IgM secreting cells were higher in c-section infants in their first year of life compared to vaginally delivered infants, indicating that c-section infants are more likely to have excessive antigen exposure across a more vulnerable gut barrier [19]. Further, studies have shown that when infants delivered via c-section are given probiotic supplementation, the rate of respiratory infections and inflammatory conditions markedly decreased throughout a period compared to those delivered via c-section who were not given probiotics [21,22].

Study of interest: A preponderance of studies has demonstrated a correlation between adverse health outcomes later in life and infants delivered via c-section compared to vaginal delivery. However, the evidence base on this correlation is currently heterogenous at best regarding conclusions, and therefore, high-quality studies are needed to ascertain the potential etiologic role of c-section delivery. Given the enormous burden of disease and the broad spectrum of adverse effects associated with c-section delivery as explored in combination with the continuously rising percentages of births that end with c-section delivery, it is imperative that the utility of long-term preventative treatments is urgently investigated.

This paper proposes a randomized control trial and longitudinal study to be initiated in order to properly evaluate the efficacy of a new method of promoting appropriate microbiome development, specifically through vaginal seeding. This novel treatment is a means of constructing a healthy microbiome within neonates delivered via c-section. In vaginal seeding, a cotton swab is first inserted into the mother's vaginal canal to

be colonized; the swab would then be inserted into the neonate's mouth and brushed across the neonate's skin. The study would evaluate the rates of autism, ADHD, asthma, inflammatory bowel disease, obesity, autoimmune disorders, atopic disorders, and metabolic disorders observed throughout the lifespan of the neonate. The results would be compared between vaginal delivery, c-section delivery with standard post-partum care, and c-section delivery with vaginal seeding.

There is currently an existing correlation between health status and neonate delivery methods that has been attributed in large due to neonates delivered via c-section not receiving proper contact with maternal vaginal microbiota. It is because of this noted correlation that this study aims to further explore this relationship in a prospective cohort study between these two groups in addition to assessing the potential benefits of vaginal seeding in comparison. This study intends to compare the short-term and long-term health status and microbiota profile of infants delivered in the United States via vaginal delivery, cesarean section, and cesarean section with vaginal seeding over the course of 2 years (24 months).

As it has been proven that neonates born via cesarean delivery are at a higher risk of selected health deficits, vaginal seeding is a proposed inoculation method designed to aid in closing this gap between the two groups' health status. By providing neonates born via cesarean section with vaginal seeding immediately following birth, it is expected that there will be an increase in favorable health outcomes and overall health status of this group compared to that of cesarean section alone.

Methodology: The goal of this study is to follow three cohorts of infants born via different delivery methods (vaginal, cesarean, and cesarean with vaginal seeding) for the first two years of life. After being screened for any transmissible diseases that would meet the exclusion criteria, the vaginal seeding group would be selected based upon the mother's consent to swab their external cervical os, vaginal canal, and vulva to then culture the neonate's mouth, eyes, ears, and nasal passages immediately following delivery. All three groups would be recruited by consenting to observational study, including possible physical exams, bloodwork, and cultures at the specific intervals of 1 day, 1 week, 1 month, 3 months, 6 months, 12 months, and 24 months. The vaginal delivery and cesarean delivery groups would be decided based solely on the natural course of events during delivery. This study would be designed to track health changes and gut microbiota related to the available data, including but not limited to neuropsychiatric, respiratory, gastrointestinal, and cardiac disorders. As associations have been made between vaginal and cesarean delivery in terms of these health markers, there have not been any clear associations made regarding these health markers in neonates who undergo vaginal seeding. Thus, the best way to understand this association (if any) is to track all three cohorts and compare overall health statuses.

Alternative methods: In general, this study may be categorized as a qualitative study as it is intended to track specific health changes with time. If this study were to be shifted into a quantitative study, one method that may still address the same issue without many details would be to track the number of times the infants needed to see a healthcare professional outside of the follow-up appointments. Further, these appointments could also be tracked based on of what body system the participant had an issue with, which warranted the visit. This way, it could be visualized by the number of times healthcare visits were made and for what category it falls under (i.e., head/neck, stomach, respiratory, general illness, anatomical, skin, reproductive, blood, etc.). Having this shift in the research question would not necessarily take away from the goal of filling the gap in the literature; instead, it may only provide a less detailed account of the differences intended to visualize.

Data collection: Although there could be many methods to collect data in this study, the study methods must remain as non-invasive as possible. As stated, the sampling frame will include three cohorts of infants born via different delivery methods (vaginal, cesarean, and cesarean with vaginal seeding) for the first two years of life. The intervals at which follow-up appointments will occur include 1 day (post-partum), 1 week, 1 month, 3 months, 6 months, 12 months, and 24 months. Data will be primarily collected through periodic follow-up appointments at each interval, intended to conduct patient interviews through the infant's primary caregiver(s). Interviews will follow standard neonatal and pediatric protocols to detect abnormalities in the child's physical, mental, or physiological development. Collecting oral and nasal swabs and a stool sample to culture microorganism strains will be imperative during each interval. Additionally, small blood samples must be collected at the 6-month, 12-month, and 24-month interval points to check for blood cell counts, hormone levels, and allergies.

This data must be tracked using a secure, password-protected Electronic Health Record (EHR) management system by the physicians, allowing data from interviews, lab results, physician notes, radiology reports, etc., to all be collected in one central location. This data can then be exported and blinded before statistical analysis occurs. Essential instrumentation required would include sterile collection swab kits, stool sample collection kits, Phadia 250, light microscopes, glass microscopy slides (with covers), hemocytometers, interview checklist forms, infant blood pressure cuffs, stethoscopes, otoscopes/ophthalmoscopes, tuning forks, pen lights, tailor's tape, Tromner reflex hammer, EHR management system, and computers.

Discussion

Social change: Assuming the results indicate a strong correlation of vaginal seeding to healthier children, many aspects of social and healthcare dynamics could potentially change. Firstly, it would become clear that vaginal seeding should soon become the new standard practice when delivering neonates via cesarean section, assuming similar trials produce comparable results. Secondly, this would slowly create a generation of healthier children, and thus, healthier adults. Lastly, having a generation of healthier individuals would significantly decrease the disease burden on the population in which this practice is used.

One of the most significant challenges in the current state of healthcare is the decision to allocate resources to medical care and research [23]. The goal of this challenge is to maintain and improve the quality of life and life expectancy in respective populations [23]. The irony of this goal is that as these parameters improve, allocating resources becomes more complex [23]. As individuals live longer, there becomes a greater risk of the burden of disease potential, consequently creating a further scarcity of healthcare resources to continue improving life expectancy and quality of life [24]. This cycle will likely continue until more advancements are made in preventative medicine, as preventing diseases can decrease the likelihood of an individual needing more healthcare resources [24].

This study aims to identify a new method of future disease prevention, decreasing the disease burden in a population overall without creating a further scarcity of resources. If the study is successful in its goal, the implications for social and healthcare change would be drastically improved as the new standard of practice would be provided regardless of age, sex, socioeconomic status, or any other parameter. By delivering this standard preventative care in all cesarean births, all sexes, races, and socioeconomic classes have the same potential to live healthier lives.

Limitations: The anticipated limitations of this study will likely come from the sample sizes of the cohorts and the loss of follow-up. This study is likely to be met with apprehension and potential skepticism by expecting mothers. Therefore, the recruitment process may take time to have enough participants even to begin the study itself. Additionally, as these cohorts will be followed over 24 months, there will be expected to be loss to follow-up, causing some bias and skew in the data. The study would do its best to keep the participants motivated and engaged; however, two years is a long time to expect perfect results from participants. The other potential limitation is that as this study plans to track a myriad of health outcomes, it may be difficult to distinguish the cause(s) of certain variables. For example, suppose a child of a mother who has pre-existing asthma develops asthma themselves. In that case, it may be difficult to draw definitive conclusions as to whether it is due to being born via c-section, due to familial inheritance, allergen by pets at home, etc.

Conclusion

Innumerous studies have showcased how the vaginal microbiome is critical in the healthy development of infants well into adulthood. Studies have also explicitly presented evidence proving that neonates delivered by cesarean section have little to no exposure to the mother's vaginal mucosa and the beneficial organisms it contains. Many of these studies have outlined specific diseases to which cesarean-delivered infants were seen with higher rates of occurrence, such as intestinal and respiratory infections, ADHD, autism, asthma, obesity, diabetes, allergies, dermatitis, inflammation, immune susceptibility, and much more. This study posits that by seeding cesarean-delivered neonates with their mother's vaginal mucosa, there is a potential to have a deeper understanding of the relationships between a mother's vaginal mucosa microflora and the development of disease and overall health status in their offspring. This proposal provided several considerations for future studies involving the vaginal seeding of cesarean infants and the comparison in health outcomes between vaginal births and cesarean sections without seeding at the 1-day, 1-week, 1-month, 3-month, 6-month, 12-month, and 24-month intervals. This qualitative study provides the opportunity for a change in the standard practice of cesarean section deliveries, which may shed light on a new method of preventative medicine seldom explored, potentially creating a new generation of healthier individuals and lowering the overall disease burden within a population.

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