

# The Effect of COVID-19 Pandemic on the Infants' Microbiota and the Probability of Development of Allergic and Autoimmune Diseases

Saba Ebrahimi<sup>a</sup> Saghi Khatami<sup>a</sup> Mehrnaz Mesdaghi<sup>a, b, c</sup>

<sup>a</sup>Department of Immunology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran;

<sup>b</sup>Department of Allergy and Clinical Immunology, Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran; <sup>c</sup>Clinical Research Development Center, Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

## Keywords

Gut microbiota · Neonates · Microbiome · Allergy · Autoimmunity

## Abstract

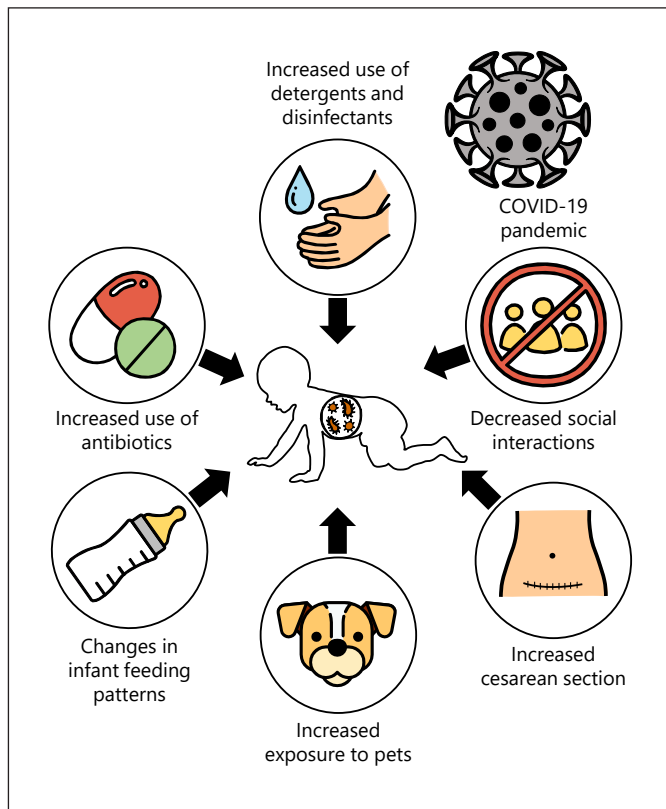
The human microbiota plays a significant role in various mechanisms of the body. The formation of a healthy microbiota, especially in early childhood, has a significant effect on maintaining human health. Since the onset of coronavirus disease 2019 (COVID-19), the disease has caused many changes in human life. According to the available information, many of these factors affect the composition and diversity of the body's microbiota, so this pandemic may alter and disrupt the microbiota and consequently increase the incidence of other diseases such as allergic and autoimmune disorders, especially in children and infants born in this era. In this review, the probable impact of the COVID-19 pandemic on body's microbiota and its relationship with the emergence of future diseases is discussed.

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Saba Ebrahimi and Saghi Khatami are co-first authors.  
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## Introduction

Since the onset of coronavirus disease 2019 (COVID-19) epidemic and its spread around the world, this disease has had a significant impact on various aspects of the life of individuals and communities and has caused changes in lifestyle, social interactions, eating habits, etc. "Microbiota" refers to microorganisms that live in various parts of the human body such as the skin, mouth, respiratory system, and gastrointestinal tract [1, 2], which weighs about 1.5 kg and is composed of >100 trillion microorganisms [2, 3]. It has been found that the most important time of exposure to environmental microbial species and nonharmful commensal microbes is during pregnancy, childbirth, and the first months of infancy [4, 5]. Numerous factors such as delivery mode, nutrition, lifestyle, and living environment affect the composition and diversity of microbiota in children [6]; therefore, lifestyle changes caused by the COVID-19 pandemic can also change the microbiota (shown in Fig. 1). Interactions between the human body and microbiota are extensive and include the regulation of immune responses [7], maintenance of safe intestinal homeostasis, and disease modification [8]. Microbial colonization at the beginning of life



**Fig. 1.** Different factors affecting the formation of microbiota in neonates during COVID-19 pandemic.

plays an essential role in the development of innate and acquired immune systems [9, 10]. The formation of healthy gut microbiota leads to T helper type 1 (Th1) cells dominance in Th1/Th2 balance [11], while a change in the homeostasis of the host microbiota can shift the Th1/Th2 cytokines balance toward the Th2 responses [12]. Numerous studies have shown the relationship between the composition and diversity of gut microbiota and its effect on the incidence of allergic diseases in infants and children [13–15]. Cytokines produced by Th2 cells, especially interleukin 4 (IL-4) and IL-5, are associated with many allergic diseases such as asthma and allergic rhinitis, and IL-4 is the major cytokine that increases IgE production [16]. In addition, many autoimmune diseases have been associated with alterations in the composition and diversity of the body's microbiota [17–19]. Since changes in the body's microbial composition may lead to loss of immune tolerance, the human microbiome appears to play a key role in the development of autoimmune diseases [20, 21]. If tolerance mechanisms are not completely effective, microorganisms can elicit immune responses against the host body [22–24]. In this review,

we investigate the effects of the COVID-19 pandemic on the microbiota of pregnant women and their infants and the possibility of increasing the incidence of allergic and autoimmune diseases in children born during the COVID-19 pandemic.

### *The Effect of COVID-19 Pandemic on Mode of Delivery*

The time and mode of delivery are important and influential factors in the composition of gut microbiota [25]. Cesarean section is increasing worldwide [26, 27], but it has several complications for both mother and child [27, 28]. The rate of cesarean section in women infected with COVID-19 is even higher than the general population [29]. In a study of 108 pregnant women with COVID-19, cesarean section accounted for 92% of all deliveries, and only 8% of participants in this study had vaginal deliveries [30]. In another study, all pregnant patients with COVID-19 pneumonia were delivered by cesarean section [31]. Among the reasons for cesarean section in women with COVID-19 were worsening of the mother's condition, severe preeclampsia, history of cesarean delivery, and fetal distress [31, 32]. In addition, concern about the risk of mother-to-child virus transmission during vaginal delivery has been another reason for cesarean section [32]. It has been observed that in infants, who are born by cesarean section (instead of vaginal delivery and crossing the birth canal, i.e., colonized with the maternal microbiota), the gut microbiota is formed with delay, and its colonization has a pattern similar to that of the mother's skin [25] (shown in Fig. 2). The study of the effect of this difference in microbiome on the incidence of allergic diseases has shown that cesarean delivery reduces microbial diversity and reduces Th1-cell responses in the early years of life [33]. Also, several research studies have linked cesarean section to the development of asthma, eczema, and allergic rhinitis [34–36]. Furthermore, some studies have shown the effect of cesarean section on increasing the risk of autoimmune diseases in children. According to a study by Sevelsted et al. [37], the cesarean section was associated with a significant increase in the risk of asthma, juvenile arthritis, and inflammatory bowel disease in children. Another study found that children born by cesarean delivery, especially the elective ones (which has been done at mothers' request, probably due to her fear of childbirth), were at higher risk for diseases related to immune dysfunction [38]. The pandemic has also affected the early days after delivery. The birth of a new baby in a family is usually accompanied by family and friends celebrating the event, but during the COVID-19 pandemic, gatherings and cel-

ebrations are strictly limited. In small gatherings, the guests are asked to use a mask, wash their hands, and maintain a distance of about 2 m with the neonate [39]. It has been observed that social relationships are associated with diversity in fecal microbiota [40]. Therefore, reducing family and friendly gatherings during the pandemic can also alter the baby's microbiome.

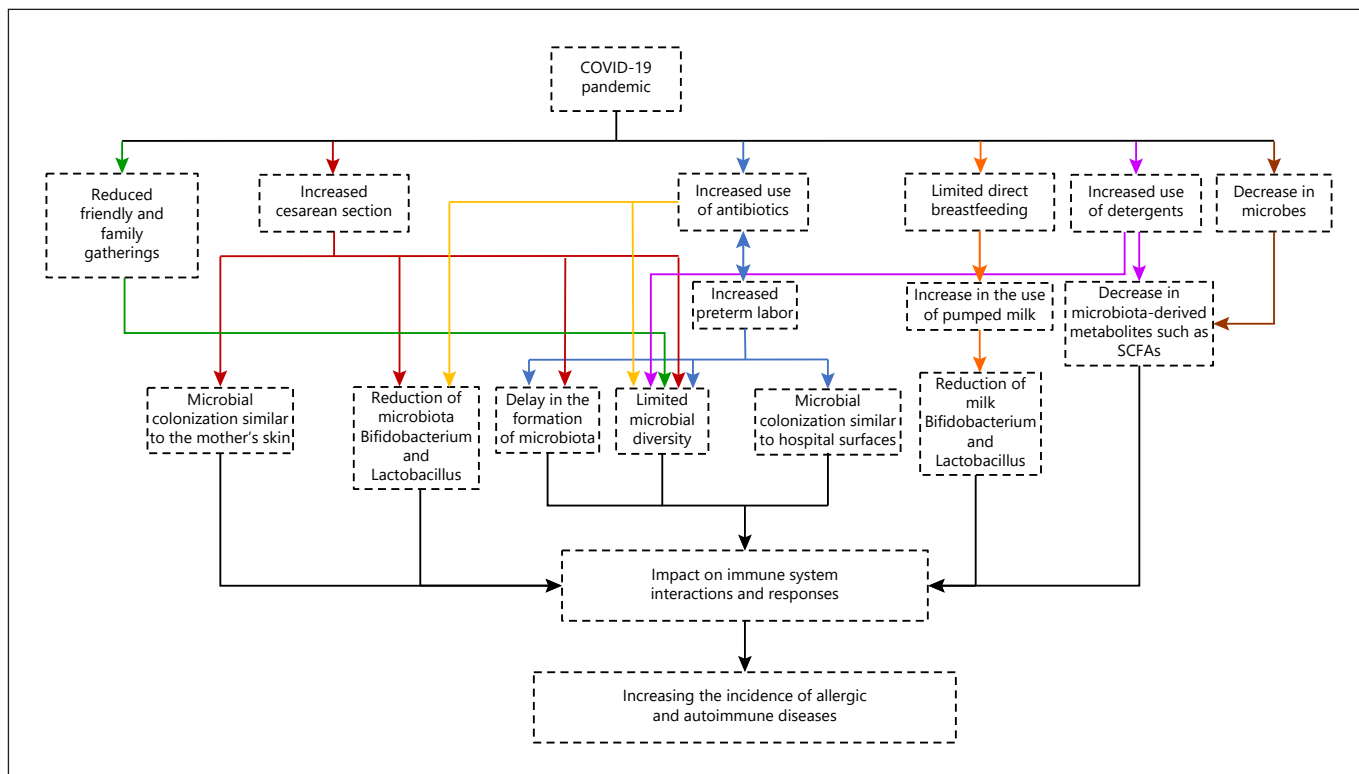
#### *COVID-19 and Infants' Feeding Pattern*

In addition to the mode of delivery, the infant's feeding pattern plays an important role in the formation of microbiota in the first year after birth [41]. Microbiota is transmitted through nonsterile breast milk [42], and breastfeeding has an important influence on the gut microbiome compared to formula feeding [43]. The mucosal immune system, in which gut microbiota are involved, suppresses immune responses to nonharmful ingested antigens [44]. Diseases caused by a deficiency in the immune system have been observed to be less common in breastfed infants [45]. The results of a study by Cardwell et al. [46] showed that breastfeeding for >3 months, or exclusively for >2 weeks after birth, is related with a 15–30% decrease in the risk of developing type 1 diabetes in children. Another study found that exclusive breastfeeding for >2 weeks is associated with a reduction in the risk of type 2 diabetes in the future life [47]. Other studies have examined the association between breastfeeding and other autoimmune diseases. The results of a study showed that breastfeeding, regardless of its duration, reduces the risk of rheumatoid arthritis [48]. Another study found that among HLA-DR4-negative infants, those who had a positive rheumatoid factor were less likely to be breastfed for >3 months compared to infants whose rheumatoid factor was negative [49]. Some studies have also shown an association between breastfeeding and a reduced risk of multiple sclerosis [50, 51]. In addition, according to the results of a meta-analysis, the risk of developing celiac disease was significantly lower in infants who were breastfed at the time of gluten intake compared with those who were not breastfed [52].

Based on the available documents, there has been no evidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the breast milk of mothers suspected to or with COVID-19 and its transmission to the infant through breastfeeding [53, 54]. Therefore, it is recommended that suspicious mothers, and even those infected with SARS-CoV-2, continue breastfeeding [55]. However, these mothers should use a mask while breastfeeding, wash their hands with soap before touching the baby, and/or use alcohol-based disinfectants [55].

#### *COVID-19 and the Use of Detergents*

Exposure to chemicals in detergents has been shown to have a significant effect on the composition and function of microbiota [56]. The metabolic activity of gut bacteria plays a vital role in the human body [57]. In one study, fecal diversity and concentration of metabolites including short-chain fatty acids (SCFAs) derived from microbiota were significantly reduced by the use of dishwashing detergents [58]. The results of a study showed that the prevalence of atopy was lower in children who had higher levels of SCFAs in their feces at the age of 1 year. In addition, these children were less likely to develop asthma and be diagnosed with allergic rhinitis and food allergies [59]. The gastrointestinal tract can communicate with the brain through metabolites produced by commensal bacteria such as SCFAs [60, 61]. In patients with multiple sclerosis, a significant reduction in the percentage of bacteria producing SCFAs has been observed [18]. Also, the presence of SCFA-producing bacteria has been shown to maintain intestinal integrity by inducing the production of appropriate amounts of mucin [62], and changes in the production of SCFAs are associated with type 1 diabetes [62, 63]. Therefore, increased usage of detergents and hand sanitizers to protect infants during the pandemic may increase the incidence of allergic and autoimmune diseases in children (summarized in Fig. 2). Many factors limit breastfeeding including the severity of the mother's illness, misconceptions by the medical team and parents about the safety of breastfeeding, hospital policy about mother and infant rooming-in after delivery, and maternal quarantine after discharge. Some mothers with COVID-19 are unable to breastfeed their infants due to the worsening of the disease, for whom, the use of pumped breast milk is recommended [55]; however, the available evidence has shown that how to breastfeed the baby (directly from the breast vs. the use of pumped breast milk) has a significant effect on the microbiota composition of milk and that indirect breastfeeding is associated with reduced milk richness and bacterial diversity [64, 65]. *Bifidobacterium* and *Lactobacillus* are the most important probiotics in breast milk [66]. Many studies have shown the reduction of atopic eczema, one of the most common types of allergies in children, after the use of probiotics [67–69]. Evidence suggests that the use of pumped breast milk reduces milk *Bifidobacteria* [64]. Also, antibiotic treatment and cesarean section were associated with a decreased amount of *Bifidobacterium* and *Lactobacillus* in the infant's microbiota [25, 70] (summarized in Fig. 2). In addition, a decrease in colonization with *Bifidobacteria* in the first year of life has been observed to be associated with allergies in children [71, 72].



**Fig. 2.** The effect of changes caused by COVID-19 pandemic on the microbiota composition and diversity.

#### *Preterm Delivery and Antibiotic Treatment*

According to studies, up to 47% of COVID-19-infected hospitalized patients give birth prematurely [73–75]. In one article, inflammation has been reported as one of the most important factors in the occurrence of preterm labor [76]. Although bacterial infections often cause the onset of inflammatory cascades and preterm labor, antibiotic use in the absence of bacterial infections has been associated with the production of inflammatory cytokines and cause cytokine storms [76]. Therefore, antibiotic treatment should not be performed by default for pregnant women with COVID-19 and can only be prescribed if necessary and after confirmation of bacterial infection in these patients [77]. However, some available evidence suggests that many pregnant patients with severe COVID-19 have taken antibiotics, although no evidence of bacterial infection has been reported [78, 79]. According to studies, maternal antibiotic treatment during and even before pregnancy has been associated with the abnormal establishment of gut microbiota in preterm infants [80, 81]. Compared to term neonates, intestinal microbial colonization of preterm infants has been found to be delayed and has limited microbial diversity [82]

(summarized in Fig. 2). In preterm infants, the composition of primary gut microbiota is similar to the bacterial composition of hospital surfaces [83]. In addition, the amount of potentially pathogenic bacteria in these infants is increased, and the amount of essential commensal bacteria is decreased [84, 85]. Premature or low birth weight infants are at the highest risk for antibiotic-related disorders because they typically receive antibiotic treatment at birth to protect them from bacterial infections and early-onset sepsis [86–88]. Antibiotic use has destructive effects such as reducing the bacterial diversity of the gut microbiota of these infants [88]. Disruption of the formation of gut microbiota by antibiotic administration may also affect the interaction with the immune system. In fact, taking antibiotics during pregnancy and after birth increases the risk of future illnesses such as asthma and other allergic diseases [89, 90]. Only a few studies have looked into the impact of preterm delivery on the microbiota of breast milk. According to these studies, the bacterial composition found in the milk of mothers, who gave birth prematurely, was different from that found in the mature milk of the same mothers, and the frequency of bacteria in premature milk was lower [91]. Monocytes transmit bacteria

from the intestine to the mesenteric lymph nodes and mammary glands via the entero-mammary pathway, which occurs in late pregnancy [92]. Therefore, this pathway may be insufficient in preterm labor and can lead to a decrease in the abundance of bacteria in breast milk.

#### *Contact with Pets during the COVID-19 Pandemic*

Numerous studies have shown that infants' contact with pets at the beginning of life and maternal contact with animals during pregnancy have a significant effect on the formation of gut microbiota in the child and can affect the incidence of atopic diseases [93–95]. In their study, Azad et al. [96] found that living with pets increased the richness and diversity of infants' gut microbiota. Another study has shown that increasing the number of pets in a child's environment in the first year of life is associated with a decrease in the prevalence of allergic diseases such as asthma and eczema at school age [97]. Due to factors such as quarantine and teleworking, keeping pets at home has increased significantly during the COVID-19 pandemic [98]. This may be in favor of preserving the diversity of microbiota and reducing the incidence of allergic and autoimmune diseases in children born during this period. However, although the available evidence suggests that the risk of animal to human transmission of COVID-19 is low [99], some pet owners abandoned their animals for the fear of transmitting SARS-CoV-2. Also, a number of people were not able to take care of their pets due to job losses and financial problems happened during the pandemic [100].

#### **Conclusion**

From the beginning of the COVID-19 pandemic, the disease has had a significant impact on human health and lifestyle. Evidence has shown that one of the important effects of this pandemic is to alter the body's microbiota and increase the risk of dysbiosis, and since pregnancy and early infancy are critical times for microbiota formation,

pregnant women and their infants are significantly affected by the condition. As numerous studies have confirmed the essential role of healthy human microbiota in regulating immune responses and maintaining body health, the changes and dysbiosis caused by the COVID-19 outbreak could increase the incidence of various disorders in the future, including allergic and autoimmune diseases, especially in children. However, due to the persistence of this pandemic and its unknown long-term effects, at the moment, the exact impact of this condition on children born during COVID-19 pandemic cannot be foreseen and needs to be clarified in future epidemiologic studies.

Based on our current knowledge about the low risk of SARS-CoV-2 transmission from pets and surfaces and the importance of proper formation of microbiota, increased infants' exposure to pets and decreased usage of disinfectants can be helpful in reducing the risk of future diseases. Moreover, mass vaccination will hopefully help returning to normal life, and having normal minimal social interactions could be the most important step toward normal formation of microbiota and immune responses.

#### **Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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#### **Author Contributions**

Mehrnaz Mesdaghi contributed to conception of the work, critical revision of the manuscript, and final approval of the manuscript. Saba Ebrahimi contributed to search of articles and data gathering, drafting of the manuscript, and final approval of the manuscript. Saghi Khatami contributed to search of articles and data gathering, drafting of the manuscript, and final approval of the manuscript.

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