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NARRATIVE REVIEW

Breastfeeding during the Covid-19 Pandemic

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ABSTRACT

Purpose of the review: The aim of the review is to delineate the role of breastfeeding by women with suspected or diagnosed COVID-19. We looked for reports that include the role of the breast-milk microbiota under the conditions of the COVID-19 pandemic.

Recent Findings: Currently, there are reports of the detection of antibodies against SARS-CoV in umbilical-cord blood and breast milk. The placenta has a very low expression of angiotensin-converting enzyme (ACE2) receptors, which appear to limit the entry of SARS-CoV-2 into the fetus.

Extract: Adequate growth and development are guaranteed by the precocious attachment of the newborn to its mother and breastfeeding in the first hour after birth, as well as the maintenance of exclusive breastfeeding in the first 6 months of life. Immunological protection against diseases is also provided, especially for respiratory and digestive diseases. In cases of mothers with COVID-19, vertical transmission from mother to child has not been documented. There is no evidence of the virus in the amniotic fluid at the time of birth or in breast milk, so it is indicated that breastfeeding should be continued but under strict compliance with safety and hygiene measures. Additionally, it has been reported that the type of delivery and its management could be involved in the spread of COVID-19 through blood, feces, and other ways.

Keywords:

MESH: Milk, Human; Coronavirus Infections; Microbiota; Infant, Newborn; Pregnancy; Breast Feeding.

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INTRODUCTION

The lactation process, bacterial communities of the vagina, and skin-to-skin contact have been shown to determine the colonization of a child's intestinal microbiota.[1] They also influence the optimal functioning of antibodies and cytosines, which are effector molecules of the immune system.[2] The initiation of breastfeeding in the first hour after birth is considered beneficial. As of 2011, the WHO recommends exclusive breastfeeding during the first six months of life since this period is considered critical for the establishment of the infant microbiota.[3] The communities that make up this microbiota will continue a transformation process during childhood depending on the stimuli to which the child is exposed in the very early stages of life.[4] In addition to protection against various diseases, the microbiota influences healthy psychological maturation.[3] For example, there is an established relationship between the intestinal microbiota and motor development, social development, and some cognitive functions during the neonatal development process.[5, 6]

With the appearance and dissemination of COVID-19 infection worldwide, there has been uncertainty regarding the potential risk of vertical transmission for pregnant and lactating women. However, the presence of the virus in the amniotic fluid has not been proven in cases of mothers with COVID-19 at the time of childbirth or in breast milk. This was confirmed by a serological study at Zhongnan Hospital in Wuhan [7] and corroborated in Ecuador by the Ministry of Public Health, [8] so there is no indication to suspend breastfeeding. Some infected women may have mild symptoms and are confined to stay at home. Others may require hospitalization.[8] Because relatively little is known about COVID-19, its effect on pregnant women and their babies is not yet well described.[9] But regardless of the mother's situation, the first hour of life is essential for the protection of the baby.

Taking into account the benefits of breastfeeding, the special influence that it has on the baby's immunological protection against viruses and other pathogens has been valued. If mothers of newborns have COVID-19 and their general condition is critical, the babies can be fed through milk banks that maintain appropriate technical conditions for collection, storage, and handling to avoid infection with SARS- CoV-2.[10, 11] There are several reasons why breast milk has a very significant protective role. It contains specific nutrients and essential biomolecules that are crucial for the development and stimulation of the child's immune system, and it contributes to their microbiota. Breastfeeding could contribute to the establishment of an anti-inflammatory microenvironment and the maturation of the immune system.[12]

Under the conditions of the COVID-19 pandemic, the mode of birth must be individualized according to gynecological-obstetric indications to avoid unnecessary caesarean sections.[9] Perinatal SARS-CoV-2 infection may be associated with adverse effects, such as premature delivery and respiratory distress in neonates.[13, 14] Thus, the management of the child should follow the protocol recommended by WHO,8 in which breast milk is prioritized as the main food for newborns due to its protective effects, although appropriate precautions must be maintained for the prevention and control of possible transmission. If the mother is separated from the baby, the colostrum supply must be guaranteed through donor mothers, which will allow for greater cellular resilience and resistance to pathogens.[15]

MATERIALS AND METHODS

A narrative review of the literature was carried out in the databases PubMed, Google Scholar, Scopus, and Cochrane Database of Systematic Reviews. The search terms were "breast milk", "Ecuador", "microbiota", and "dysbiosis". The search was limited to the last 12 years, which produced few results. The association between breast milk and COVID-19 was investigated by searching databases for studies published since December 2019 in Medline, scientific societies, the

World Health Organization (WHO), and the Ministry of Public Health of Ecuador (MSP) were used. In relation to COVID-19, original studies such as randomized trials, literature reviews, and case series were found. In addition, state guidelines and epidemiological reports were added.

INFLUENCE OF THE MICROBIOTA ON THE IMMUNE SYSTEM OF THE CHILD

At the time of birth, the immune system is immature and requires several stimuli to begin establishing a pool of functional leukocytes.[16, 17] Arrieta et al. have suggested that external factors to which the newborn is exposed during the first 100 days of life can considerably influence the development of the immune system.[18] By 14 weeks of gestation, most fetal immune cells are functional, including "natural killer" cells, T and B lymphocytes, and dendritic cells.[19] However, a dilemma lies in their ability to mount an appropriate immune response since this ability depends on not only the functionality of each cell, but also on the stimuli present that allow for the adaptation and preparation of neonatal cells to interact with each other and establish cellular communication networks.[20-22]

As an example, the adaptive system in its early stages has not had enough time to build a cellular repertoire that allows for antigen discrimination and the establishment of cellular memory. Furthermore, antigen presentation is ineffective. The innate system is in charge of defending the newborn, but cells such as neutrophils and macrophages also have a reduced capacity for phagocytosis and chemotaxis.[21] The presence and colonization of bacterial species is essential at this time since a considerable amount of stimuli will come from antigens released by the microbiota.[20, 23]

During human development, the immune system and the microbiota are deeply related since the presence of one shapes the functioning of the other, and vice versa.[16, 21, 23] Levan et al. reported that the presence of metabolites of the microbiota, such as short-chain fatty acids, can inhibit the induction of regulatory T lymphocytes by dendritic cells in vitro. This inhibitory effect is possibly associated with the development of asthma and atopic diseases in neonates. Another study carried out at the University of Sydney, Australia, associated low levels of another metabolite of the microbiota, acetate, with a reduction in regulatory T lymphocytes, as well as the architecture and the size of the thymus in neonates of preeclamptic mothers.[24, 25] Both studies indicate how the microbiota and its derivatives can play crucial roles in shaping the immune system.[23] Once the colonization process is established, the microbiota contributes to the functioning of the adult immune system, its regulation, the attainment and storage of energy, and the maintenance of intestinal homeostasis.[26]

The scientific evidence supporting the co-evolution process includes animal models in which the absence of an intestinal microbiota is associated with defects in the development of lymphoid tissue, the spleen, the thymus, and lymph nodes.[21] Germ-free (GF) murine models show reduced numbers of CD4+ cells, IgA-producing cells, and hypoplastic Peyer's patches. In these models, the lack or overproduction of a certain type of immune cell may be associated with colitis, exaggerated allergic responses, and abnormal immunoglobulin levels. When studying bacterial communities, it has been observed that several Lactobacillus species are natural activators of natural killer cells and regulators of CD4+, CD8+ T lymphocytes, and regulators.[4] Based on this evidence, it has been accepted that the maturation of the intestinal mucosa and its associated lymphoid tissues depends on intestinal bacterial colonization. [22]

The importance of the microbiota in the development of the immune system has also been demonstrated in observational studies on children born by cesarean section. This form of birth has been associated with a higher rate of asthma and allergic rhinitis in girls,[27] as well as celiac disease and gastroenteritis.[28] A study published in 2019 examined more than 800 samples of children between 6 months and 2 years of age who were born by cesarean section in Ecuador. The results showed that there were higher levels of inflammatory C-reactive protein, basophils, and a rates of symptoms than those of children born vaginally.[29] These results suggest that delivery by cesarean section can alter the

inflammatory response to infection and allergy.[29] Most importantly, this evidence also suggests that the composition of the microbiota has an essential impact on the development of functional immune systems. [21, 22].

INFLUENCE OF BREAST MILK MICROBIOTA

Breast milk contains immunoglobulins, lysozymes, cytosines, characteristic oligosaccharides, and lactoferrin.[29, 30] In general, the protein and lipid content varies over time but is always adjusted to the infant's nutritional needs.[20] An example of this is the components related to maternal cells, such as neutrophils in the blood and various types of cells, including some acinar cells, which synthesize components such as lactoferrin (Lf), an antimicrobial glycoprotein with immunomodulatory effects. This has been reported in the context of SARS-CoV in an article published in 2011 by Lang et al., which demonstrated that Lf inhibits SARS pseudovirus infection in HEK293E/ACE2-Myc cells in vitro.[31]

Immunoglobulin transfer does not only provide protection in a direct way. The glycosylation of maternal IgG occurs during the gestational period and lactation.[32] This process produces hyperglycosylated IgG, which has potent anti-inflammatory properties.

The microbiota of breast milk can actively colonize the newborn's gastrointestinal tract and promote the establishment of bacterial species that are beneficial to health.[29] This plays a fundamental role in the formation of a child's microbiota. There is evidence to support this hypothesis in studies conducted on GF mice, which show large differences in the immune system compared to normal offspring. The normal phenotype of can only be partially recovered if there is a bacterial inoculation after the period of breastfeeding, which indicates the importance of early exposure to adequate stimuli.[33]

During this short period of approximately 3 months, breast milk and its flora can be considered as promising tools for the prevention of a series of diseases. The reason is that they provide neonates with microbiota, prebiotics, and immunological factors that can influence the degree of diversity of the neonatal microbiota. Furthermore, they condition the immune system and, most importantly, prevent allergic and metabolic diseases such as obesity.[34, 35] The mother's state of health can alter the composition of the microbiota and its diversity, which has been observed in several comparative studies. For example, one study carried out by the Spanish Higher Council for Scientific Research showed that breast milk from celiac mothers has considerable less *Bifidobacterium* compared to healthy mothers.[36] Another study was carried out in areas of Mozambique with high prevalence of AIDS. The study found that breast milk from HIV+ mothers shows a decrease in *Staphylococcus sp*. and an increase in *Lactobacillus sp*.[37].

THE MICROBIOTA IN BREAST MILK UNDER THE CONDITIONS OF THE COVID-19 PANDEMIC

A connection has been established between the gastrointestinal tract and the lung microbiota, although it is not fully understood. It is known that there is microbial migration by microaspiration and inhalation of microorganisms.[38] For more than a decade, some authors have reported the possibility of detecting anti-coronavirus antibodies due to the fact that some human milk samples were positive for IgA against porcine-transmitted gastroenteritis coronavirus.[39] Currently, there are reports of antibodies against SARS-CoV (the pneumonia virus from the year 2003) in umbilical cord blood and breast milk. [40]

The Ministry of Public Health of Ecuador states that no vertical transmission of COVID-19 has been documented and that there is no evidence of mother-to-child transmission when the infection occurs in the third trimester.[7] This information is based on negative results from samples of amniotic fluid, umbilical cord blood, vaginal discharge, neonatal throat samples, and breast milk.[7, 13, 14, 41] These and other works show that Ecuador is actively working on research aimed at promoting breastfeeding as an important national strategy to contribute to the timely diagnosis and prevention of diseases in newborn children. These

efforts were generated through the Ministry of Public Health with support from the Intercultural Health sub-process.[43]

A serological study conducted at Zhongnan Hospital in Wuhan examined samples from 6 SARS-CoV-2 positive mothers and their infants. The results revealed specific IgG and IgM antibodies in the blood of newborns. The IgG concentrations in 5 of the 6 infants were even elevated compared to normal levels. IgG is known to cross the placenta at the end of the second trimester, so the acquisition of passive immunity against SARS-CoV-2 is possible. However, the transfer of IgM detected in two of the neonates is unusual because its molecular configuration prevents placental transfer.6 The placenta has been reported to have very low expression of angiotensin-converting enzyme (ACE2) receptors, which appear to facilitate the entry of SARS-CoV-2.[42] However, it is possible that the IgM was produced by the same newborn if the virus managed to cross the placenta.[6]

There is currently not enough evidence about the microbiota of breast milk from mothers infected by COVID-19 and its transmission, as well as its colonization in neonates. Thus, investigations in this regard are urgently needed. A recent study reported that breast milk samples from mothers diagnosed with COVID-19 after the first breastfeeding were negative for the virus.[13, 14] With this information, breastfeeding is not contraindicated.

The type of delivery and its management could be involved in contagion by COVID-19. It has been reported that the virus can be found in biological fluids from the patient, such as feces and blood,[43] but not in breast milk.[13, 14, 41, 44] However, non-essential cesarean births should be avoided according to an evaluation of an obstetrician-gynecologist, and if possible, normal delivery should be promoted.[45] It is recommended that infected mothers wear an N95 mask while handling and breastfeeding the baby and that they wash their hands and arms with liquid soap before taking the baby to breastfeed. Surrounding surfaces must be cleaned and disinfected. It is recognized that these aseptic measures could negatively affect the development of the baby's own microbiota,[44] but in this context, it is clear that it is more important to prevent the infection of the newborn in the first months of life with SARS-CoV-2 than to worry about the microbiota and its effects later in life.

FINAL CONSIDERATIONS

Under the conditions of the COVID-19 pandemic, birth plans by families and health personnel must be respected and complied with to the extent possible.[46] It is important to analyze the nutritional and gastrointestinal function of both the mother and the child. Possibly, the application of pre- and probiotics could reduce the risk of secondary infection due to bacterial dysbiosis. Some patients with COVID-19 were shown to decrease intestinal microbial dysbiosis by using probiotics such as *Lactobacillus and Bifidobacterium*.[47, 50]

COVID-19-positive mothers should be treated with the highest priority. The prenatal, neonatal, maternal, and family health care units should motivate and support mothers during childbirth with the guidance and support of health personnel. They should also stimulate contact and immediate attachment to start breastfeeding, recommend joint accommodation, and carry out medical discharge with adequate guidance so that successful breastfeeding can continue at home. It is also advisable to establish a line of communication to advise mothers and help solve problems that could lead to the abandonment of breastfeeding.

This process will undoubtedly have a positive impact on the symbiosis of the microbiota and on healthy growth and development. In the event of health complications of the mother, the baby should be supported through a human milk bank during the mother's hospitalization, and continue breastfeeding as soon as possible. Health units can provide support at this point in the extraction of milk, subsequent relactation, and promoting the donation of human breast milk.

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CONCLUSIONS

The COVID-19 pandemic highlights the importance of breastfeeding for its immunological, metabolic, emotional, and social benefits, among others. Many of these benefits are a consequence of the establishment and colonization of the intestinal microbiota. General measures are recommended for nursing mothers, such as hand washing and the use of a masks, but breastfeeding is not contraindicated for women with mild and moderate symptoms. Nevertheless, in health conditions that compromise the life of the mother, breastfeeding should be temporarily replaced.

ARTICLE ADMINISTRATIVE INFORMATION

Abbreviations
ACE: Angiotensin Converting Enzyme.
COVID-19: Coronavirus Disease 2019.
Lf: Lactoferrin

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