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BRIEF REPORT

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

Lactoferrin is an important factor when breastfeeding and COVID-19 are considered

The COVID-19 pandemic raises issues about breastfeeding when mothers have tested positive for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We do not know whether the virus can be passed to a foetus or baby during pregnancy or delivery, and it has not been found in amniotic fluid or breast milk.[1] Separating babies from virus-positive mothers make breastfeeding problematic and could prevent possible protection against viruses.[2] Mothers who are too sick to feed could consider expressing milk or donor human milk.[1] Lactoferrin is a protective factor in mother's milk and a key component of the mammalian innate response to infections. This whey protein has several biological functions, including binding and releasing iron. It also inhibits the growth of many pathogens, by mechanisms such as disrupting cell membranes, sequestering iron, inhibiting microbial adhesion to host cells and preventing biofilm formation.[3] Lactoferrin is very similar between species, and the homology between humans and cattle is 77%. It is produced and secreted by glandular epithelial cells, with a peak concentration in colostrum (8 mg/mL), lower levels in mature milk (3.5-4 mg/mL) and even lower levels in exocrine secretions. Levels in breast milk decrease over time, and preterm infants can receive the highest concentrations for the longest periods, which could reduce the very high risk of sepsis from intestinal and respiratory tracts. Lactoferrin's antimicrobial actions have controversially demonstrated clinical efficacy in preventing sepsis in high-risk preterm infants. Bovine lactoferrin supplements have significantly decreased late sepsis or necrotising enterocolitis in some studies,[4] but not others.[5] In vitro studies on a wide spectrum of ribonucleic acid and deoxyribonucleic acid viruses have produced intriguing results.[3] Lactoferrin inhibited both the attack and growth of the respiratory syncytial virus, interacting directly with the virus' F protein, which is the most important surface glycoprotein for viral penetration. Both bovine and human lactoferrin prevented infection in vitro in a dose-dependent manner, inhibiting the synthesis of adenovirus antigens in the first stage of infection. This happened when lactoferrin was added to cell cultures before the viral attack, interfering with the primary receptors present at the cellular level. While lactoferrin does not seem to inhibit rhinovirus replication, using bovine lactoferrin to treat influenza A virus in vitro inhibited cell apoptosis induced by viral effectors.[3]

Lactoferrin can prevent viral infections by interacting with heparin sulphate glycosaminoglycan (HSPG) cell receptors, which allow the first anchoring site on the cell surface in the first phase of virus infections and in coronaviruses in particular. After anchoring, the viruses accumulate on the cell surface and recognise more virus-specific receptors. These include the angiotensin-converting enzyme 2 (ACE2) receptor, a metallopeptidase that can hook the virus terminals and facilitate entry into the cell.[3,6] These mechanisms were seen in the 2002 SARS-CoV epidemic and are almost the same for SARS-CoV-2. We know that SARS-CoV-2 can enter cells through ACE2 receptors on the surface of the cell membrane. Lang et al found that lactoferrin interfered with how SARS-CoV entered human cultured cells. It inhibited the infection by competitively localising to the virus anchoring sites provided by HSPGs, preventing the preliminary contact between the SARS-CoV and host cells. Lactoferrin blocked the interaction between spike viral protein and HSPGs in an ACE2-independent fashion. This mechanism significantly interfered with viral anchoring and prevented the subsequent mechanisms that allow the viral concentration on the cell surface, as well as the contact with the specific entry receptors, namely ACE2, that results in the full infection.[6]

While SARS-CoV-2 is thought to mainly transmit via respiratory droplets, it can invade enterocytes, causing symptoms and acting as a reservoir. Gastrointestinal symptoms can be the first clinical manifestation in infants.[7] Furthermore, early breast milk and lactoferrin can promote a local gut environment, namely microbiota plus tight junctions, that reinforces the innate defences of neonates. Lactoferrin promotes the growth of favourable gut microbiota and the proliferation of enterocytes with direct anti-inflammatory and immunomodulatory actions. These maintain and reinforce mucosal immunity and the gut epithelial barrier. These effects and mechanisms have not been tested on SARS-CoV-2, but clinicians could consider this approach, as they have affected other coronaviruses. Most (79%) of the SARS-CoV and SARS-CoV-2 have identical sequences, and their receptor-binding domain structure is also very similar.

We believe that breast milk, particularly lactoferrin, demonstrates potential antiviral effects. The challenge is how effective they are at preventing viral infections, like coronaviruses. The way lactoferrin acts on cell receptors prevents viral anchoring, surface accumulation and cell entry. Further clinical evidence is needed, but we believe that early breastfeeding provides vital prevention during viral epidemics, due to the high value of colostrum and breast milk and the specific role of lactoferrin.

CONFICT OF INTEREST

None.

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