A human milk perspective on the transmission of maternal factors to her child

Focus on stress, nutrition and immunity

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Antibodies Against SARS-CoV-2 in Human Milk: Milk Conversion Rates in the Netherlands

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Abstract

Background

It has been demonstrated that human milk from mothers who have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) contains antibodies against the virus, which could play an important role in protecting the recipient infant against coronavirus disease 2019 (COVID-19). Seroconversion is measured frequently around the world, but the milk conversion rate is unknown.

Research Aims

To determine (1) the prevalence and (2) the dynamics of immunoglobulin A (IgA) antibodies against SARS-CoV-2 in human milk amongst lactating mothers in the Netherlands.

Methods

In this large prospective cohort study, lactating mothers (N = 2312) were included between October 12, 2020 and February 24, 2021. Enzyme-linked immunosorbent assay was used to determine levels of IgA antibodies in human milk and immunoglobulin G (IgG) antibodies in serum against the ectodomain of the SARS-CoV-2 spike protein.

Results

A total of 691 (30.6%) participants had SARS-CoV-2 specific antibodies in human milk and/or serum. Of these participants, 524 (23.1%) had IgA antibodies against SARS-CoV-2 in human milk, and 356 (15.7%) had IgG antibodies against SARS-CoV-2 in serum. A total of 199 (8.8%) participants had antibodies in both human milk and serum. SARS-CoV-2 specific IgA antibodies in human milk remain present at least 10 months after a polymerase chain reaction confirmed infection.

Conclusion

The prevalence of IgA antibodies against SARS-CoV-2 in human milk was 23.1% in our cohort. This high prevalence of antibodies in human milk might lead to passive immunity in many breastfed infants and may serve as protection against COVID-19.

Background

The coronavirus disease 2019 (COVID-19) pandemic emerged in December 2019 (1). It rapidly became a public health emergency of international concern due to its high dispersion rate influencing public health, society, and the economy across the world (2). Therefore, the World Health Organization declared the outbreak a pandemic on March 11th, 2020.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is part of the *Coronaviridae* family and causes COVID-19. Transmission between humans occurs mainly through droplets caused by sneezing or coughing or inhalation of aerosols, which are subsequently picked up by other people (2). The disease has a wide range of clinical presentations, from asymptomatic infection or only experiencing cold-like symptoms to severe pneumonia, hospital admission, or even death (2).

In general, people with an impaired immune function, like the elderly, experience the most severe symptoms of COVID-19. Newborn infants also have an impaired immune function due to the lack of a fully developed immune system, and therefore, they may be seriously affected by SARS-CoV-2, although usually mildly (3-8). Human milk is considered the main source of passive and active immunity for newborns and infants, as it contains a large array of bioactive factors, including antibodies, oligosaccharides, nucleic acids, and cytokines, that help enrich an infant's immune system (9). In the first six months of life, breastfed infants have a 2.2-fold lower mortality risk due to fewer infections than non-breastfed infants (10). This highlights the protective effects of human milk against infectious diseases.

The most abundant antibody in human milk is immunoglobulin A (IgA), comprising approximately 90% of the total immunoglobulins (11, 12). IgA in human milk is mostly polymeric and bound to a secretory component (13). In general, IgA antibodies in human milk confers protection for the infant by eliminating invading pathogens through its inhibiting effect to bind to host-receptors of intestinal epithelial cells or entrapping microorganisms within the mucus (11). Specific IgA antibodies have been identified in human milk of previously infected mothers against various viruses, including SARS-CoV, human immunodeficiency virus (HIV) and respiratory syncytial virus (11, 14).

Much data is available on the prevalence of seroconversion throughout the world, mainly measured by blood banks collecting samples from their regular donors. Seroconversion rates range from 0.02% to 53.40%, depending on the prevalent of SARS-CoV-2 infection in specific regions (15). In the Netherlands, seroconversion in donors from our national blood bank (Sanquin) reached between ten and fifteen percent at the end of

2020 (16). Lactating mothers comprise a specific group whose behavior might be more self-protecting compared to the population that donates blood due to pregnancy or care for a newborn child.

There is limited evidence regarding the presence of antibodies against SARS-CoV-2 in human milk. However, it has been demonstrated that human milk from mothers who had previously been infected contains SARS-CoV-2 specific antibodies and these antibodies were capable of neutralizing the virus in small sample sizes (17-19). Since lactating mothers with COVID-19 hardly infect their infants, a protective role of human milk in the context of this infectious disease is suggested (20). Breastfeeding has been documented safe under certain conditions, including measures to reduce the risk of transmission among which wearing a face mask and washing hands. To date, replication competent SARS-CoV-2 has not been isolated from human milk and transmission of the virus to the infant through human milk has not been reported (19, 21-23). Despite the discovery of viral particles in human milk, breastfeeding was not associated with SARS-CoV-2 infection, suggesting that viral transmission through human milk, if any, is very rare (22).

Antibodies against SARS-CoV-2 have been demonstrated in human milkin small sample sizes, larger studies regarding IgA against SARS-CoV-2 in human milk are lacking. As human milk antibodies can play an important role in child immune function and subsequently child health, this study aims to determine the prevalence and dynamics of IgA against SARS-CoV-2 in human milk amongst lactating mothers in the Netherlands.

Methods

Research design

The COVID MILK – POWER MILK study is a prospective cohort study. To determine the prevalence of IgA antibodies against SARS-CoV-2 in human milk of lactating mothers in the Netherlands, a large amount of samples was collected. The study was approved by the Ethics Committee of the Amsterdam University Medical Centre, VUmc on September 28th, 2020 (NL74752.029.20).

Setting and Relevant Context

In the Netherlands, approximately 170,000 infants are born annually (24). Breastfeeding, feeding human milk to the infant, is highly recommended after birth; approximately 70% of mothers start breastfeeding. After six months, 20% of these mothers are still breastfeeding their child (25).

Sample

Lactating mothers were recruited through the media (e.g. social media, television, newspapers and radio). All lactating mothers were eligible to participate. There were no exclusion criteria. In total, 9239 lactating mothers were interested in participation. After screening, 8644 lactating mothers were eligible to participate in the study and received the study information letter. At time of analysis, a total of 2312 participants were included in the study (Figure 1). This sample size is assumed to be adequate to answer the research question.

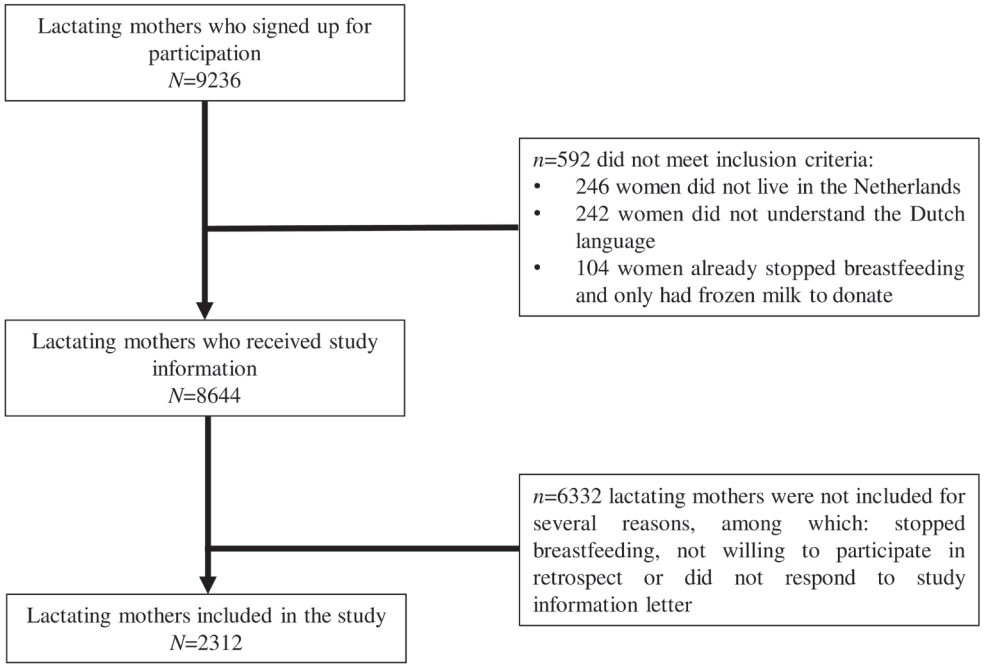

Figure 1: PRISMA of the study population

Measurement

To obtain information on participant characteristics, a Dutch questionnaire was sent to the participants. Before analysis, the collected human milk and serum samples were stored at the Amsterdam UMC, location VUmc, at -80°C. To assess the SARS-CoV-2 specific IgA antibodies in human milk and IgG antibodies in serum, an enzyme-linked immunosorbent assay (ELISA) with the SARS-CoV-2 spike protein was used, as described previously (17). Soluble perfusion-stabilized spike protein of SARS-CoV-2 was generated and immobilized overnight on a 96-well plate (Greinier) using 0.1M NaHCO3 followed by a 1-h blocking step with 1% casein Phosphate Buffered Saline (PBS) (Thermo Scientific). The human milk samples were diluted at 1:10, and the serum samples 1:50 in 1% casein PBS (Thermo Scientific) and incubated on the spike protein coated 96-well plates, for

2-h to allow binding to the target protein. Finally, a 1:3000 diluted horseradish peroxidase (HRP)-labeled goat anti-human IgG (Jackson, Immunoresearch) in 1% casein PBS was used to detect specific IgG antibodies in the serum samples. In contrast, a 1:5000 diluted HRP-labeled goat anti-human IgA (Biolegend) in 1% casein PBS was used for the human milk samples. After 1 hour incubation, 3,3',5,5'-Tetramethylbenzidine (TMB) was used for the read-out at 450nm. For the determination of the cut-off value, a relative operating characteristic curve analysis was performed for both milk and serum samples using pre-pandemic negative samples and polymerase chain reaction (PCR) proven positive samples. The milk samples were considered positive at an optical density (OD) 450nm cut-off value of 0.502 and 0.452 for the serum samples. With these cut-off values, the sensitivity was 67.9% (95% confidence interval (CI): 61.0–74.1%) for IgA antibodies in human milk with a specificity of 99.0% (95% CI: 94.7–100.0%) and for serum IgG antibodies the sensitivity was 95.9 (95% CI: 92.9–97.6%) with a specificity of 99.1 (95% CI: 94.9–100%).

Data collection

Data collection took place between October 12th, 2020 and February 24th, 2021 and written informed consent was obtained prior to sample collection from all participants. Participants were requested to collect human milk of the first feeding moment on the morning of their study appointment. They were instructed to empty one breast in the morning before feeding their child. After mixing the milk, 10-30 mL was donated in a sterile container (SteriFeed®) that was provided by the researchers and subsequently store the collected human milk in the refrigerator at 2□8°C. To assess the prevalence of serum immunoglobulin G (IgG) antibodies against SARS-CoV-2, a phlebotomist performed a venipuncture and collected a 5 mL vial of blood during the study appointment. Participant characteristics were obtained by a questionnaire. All scientific information collected as part of this study was treated confidentially and made pseudonymised by assigning a unique code to each study participant and stored safely at the study side.

Data analysis

Statistical analyses were performed by using IBM SPSS Statistics for Windows, version 26. Characteristics were described in descriptive statistics including frequencies or median with interquartile ranges (IQR), depending on the distribution. Graphpad Prism 8.2.1. for Windows was used to display the prevalence and the dynamics of IgA antibodies in human milk and IgG antibodies in serum over time. To test the difference in prevalence of SARS-CoV-2 specific antibodies over the different months, a Chi-square test was performed.

Results

A total of 2312 lactating mothers participated in the study, providing 2276 human milk samples and 2267 serum samples and 2294 participants completed the questionnaire. The participant characteristics are depicted in Table 1. Of the participants, 165 (7.3%) had a previous PCR confirmed SARS-CoV-2 infection, on average 8 weeks before sample collection. Of those participants, 159 reported symptoms, of which a runny nose (*n*=121), fatigue (*n*=121), headache (*n*=110), loss of smell (*n*=110), were the most reported. Fever was reported 87 times. None of the participants received a SARS-CoV-2 vaccine prior to participation.

Table 1. Participant characteristics.

Participant characteristics	Total	Positive for SARS-Cov-2 sIgA	Negative for SARS-CoV-2 sIgA
Age mother years* (SD)	33.1 (3.8)	33.3 (3.9)	33.1 (3.8)
Body Mass Index** (IQR)	23.3 (21.3,26.0)	23.2 (21.2,25.9)	23.4 (21.3,26.1)
Comorbidities no (%)	306 (13.8)	66 (13.1)	237 (14.1)
Autoimmune disease no (%)	72 (3.2)	11 (2.1)	61 (3.6)
Smoking no (%)	42 (1.9)	11 (2.2)	30 (1.8)
Infant			
Age infant weeks** (IQR)	34 (24,50)	40 (27,63)	32 (23,47)
Gestational age at birth weeks** (IQR)	40 (39,40)	40 (39,40)	40 (39,40)
COVID-19			
Positive PCR test no (%)	165 (7.3)	98 (19.2)	61 (3.6)
Weeks post positive PCR** (IQR)	8 (3,15)	9 (4,17)	7 (3,14)

Abbreviations: sIgA: secretory Immunoglobulin A, PCR: polymerase chain reaction, SD: standard deviation, IQR: interquartile range, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, COVID-19: coronavirus disease 2019
* = mean
** = median

Of the participants, 691 (30.6%) had SARS-CoV-2 specific antibodies in human milk and/or serum, of whom 524 (23.1%) only in human milk, and 356 (15.7%) only in serum. A total of 199 (8.8%) participants had SARS-CoV-2 specific antibodies in human milk and serum (Figure 2). Figure 3 demonstrates the prevalence of SARS-CoV-2 specific antibodies in human milk and serum overtime during the study period. The prevalence of human milk SARS-CoV-2 specific IgA antibodies increased during the study period ($p<0.001$), whereas the prevalence of serum SARS-CoV-2 specific IgG antibodies showed a more variable pattern with increases and decreases ($p=0.011$). Of the participants with SARS-CoV-2 specific IgA antibodies in human milk, 427 (81%) have had COVID-19 related symptoms.

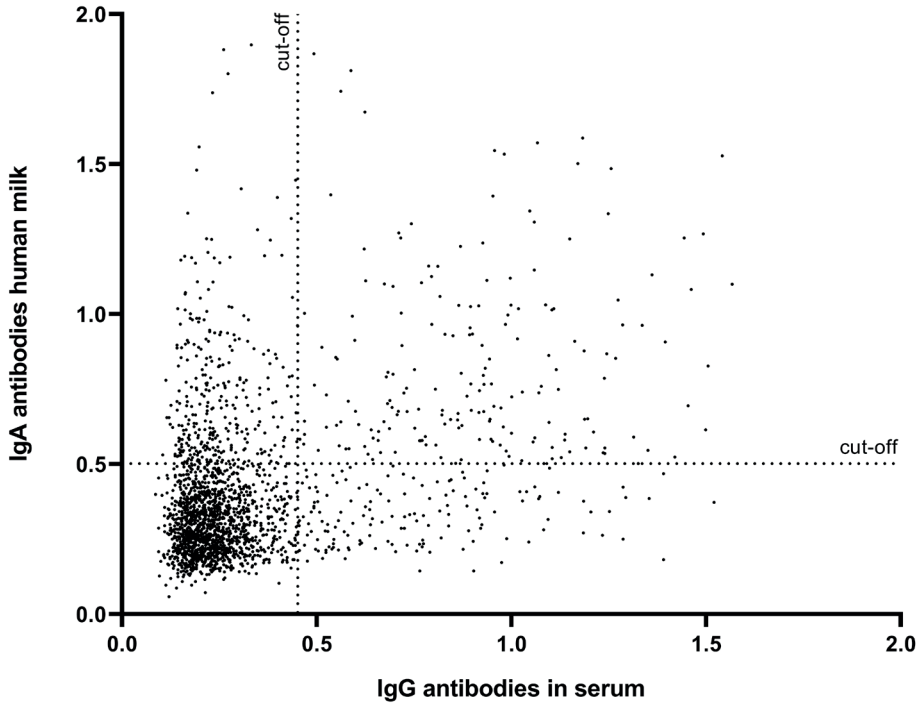

Figure 2: SARS-CoV-2 specific antibody levels in human milk versus serum
Abbreviations - IgA: Immunoglobulin A, IgG: Immunoglobulin G, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

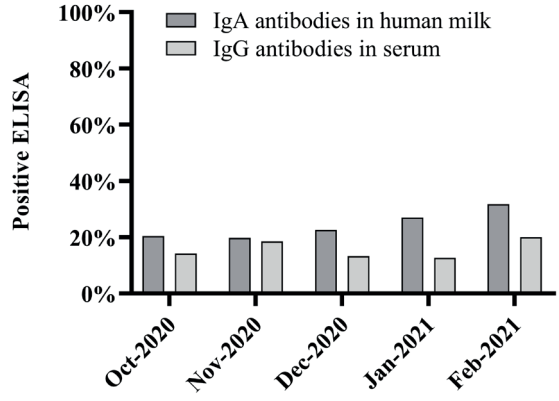

Figure 3: Prevalence of SARS-CoV-2 specific antibodies over the study period
Abbreviations - IgA: Immunoglobulin A, IgG: Immunoglobulin G, ELISA: Enzyme-linked immunosorbent assay

Figure 4 demonstrates the dynamics of SARS-CoV-2 specific IgA antibodies in human milk of those participants who recovered from PCR confirmed COVID-19. It is demonstrated that these antibodies remain stable over time. SARS-CoV-2 specific IgA antibod-

ies in human milk remain present up to at least 10 months after infection. Out of the 165 participants that had a previously proven SARS-CoV-2 infection by PCR, 98 (59%) participants showed SARS-CoV-2 specific IgA antibodies in their milk. In 61 (37%) of the 165 PCR confirmed SARS-CoV-2 infected participants, IgA antibodies were not detected in their milk, which is consistent with the lower sensitivity of the ELISA for milk samples.

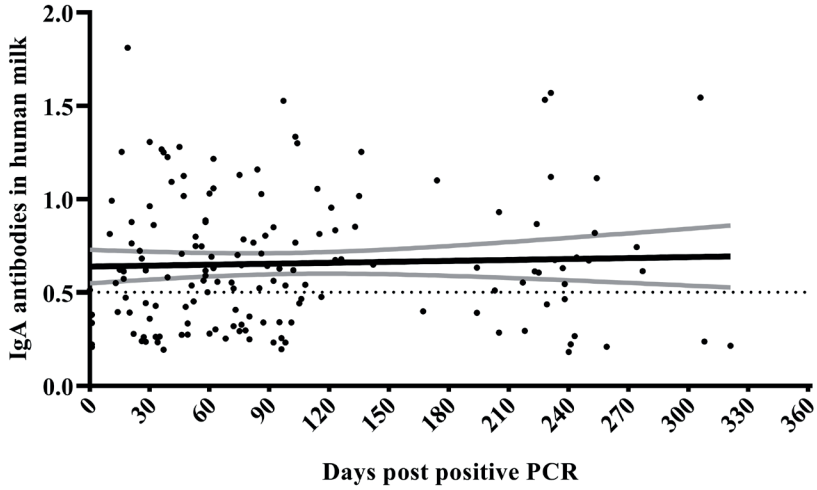

Figure 4: Dynamics of SARS-CoV-2 specific sIgA in human milk in lactating mothers who recovered from PCR confirmed COVID-19
Curved lines represent the 95% confidence interval.
Abbreviations - IgA: Immunoglobulin A. PCR: polymerase chain reaction, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, COVID-19: coronavirus disease 2019

Discussion

The prevalence of IgA antibodies against SARS-CoV-2 in human milk was 23.1% and in serum, the prevalence of IgG antibodies against SARS-CoV-2 was 15.7%. The bloodbank of the Netherlands (Sanquin) reported a seroprevalence of SARS-CoV-2 in their blood donors of 2.7% 1 month after the start of the pandemic (26). From October 2020 until February 2021, ten to fifteen percent of the blood donors showed antibodies (16). Presumably, the difference in prevalence with our study cohort is due to an overrepresentation of the actual prevalence, as lactating mothers with previous symptoms of COVID-19 might have been more likely to participate in this study.

Whereas some participants who had tested positive showed antibodies in both human milk and serum, in most of them, SARS-CoV-2 specific antibodies were found only in human milk or serum. In previous studies in SARS-CoV-2 infected patients, serum and mucosal IgA antibodies have been detected earlier in the immune reaction than serum

IgG antibodies (27), suggesting that the systemic IgG antibody response might be slightly slower compared to the mucosal IgA antibody response. After a rapid early IgA antibody response, a decline in IgA antibody serum levels was observed earlier than a decline in serum IgG antibodies. Therefore, IgA antibodies seems to play an especially important role during early SARS-CoV-2 infection (27).

Much of our population had not been tested for SARS-CoV-2, even though most of them experienced several episodes of mild symptoms that could be attributed to COVID-19 or other infectious diseases. Consequently, we were not able to determine the time between SARS-CoV-2 infection and time of sampling within this study for many of the participants with detectible SARS-CoV-2 antibodies. It might well be that participants who only showed IgA antibodies in human milk were more likely to have been included closely after their SARS-CoV-2 infection, whereas participants only showing IgG antibodies in serum were more likely to be included further from the moment of infection. Moreover, the severity of symptoms might have influenced the duration of stay of antibodies in human milk (28).

A higher background was observed during the analysis of human milk samples, especially for some samples, which might be explained by non-specific reactivity. This could be due to the viscousness of human milk samples and the limited dilution possibilities because of lower antibody concentrations compared to serum. The high background might lead to an overestimation of the actual prevalence due to false-positive samples. To minimize false-positive samples, a cut-off specificity level of 99% was used.

One of the strengths of this study is the large sample size, which increases the possibility of obtaining an accurate representation of the prevalence of SARS-CoV-2 specific antibodies in the Netherlands. Another strength is the standardized way of milk sampling. Since hindmilk contains more fat than foremilk, and antibodies are more prone to bind to fat (29), it is important to collect human milk samples in a standardized way. Therefore, our participants received clear instructions on timing and human milk collection methods, to avoid variation in antibody levels due to sampling issues.

Limitations

Our study might be limited by a selection bias. Lactating mothers could sign themselves up for participation, which might lead to a misrepresentation of the actual prevalence of antibodies in lactating mothers, as mothers with symptoms may have signed up more frequently than mothers without symptoms. Furthermore, in the first months after the outbreak of SARS-CoV-2, the testing capacity in the Netherlands was limited, restricting the determination of the dynamics of SARS-CoV-2 specific antibodies in confirmed cases over time. In the future, researchers should incorporate not only the presence

of SARS-CoV-2 specific antibodies in human milk, but also the maturation, affinity and functionality of these antibodies.

Conclusions

The prevalence of IgA antibodies against SARS-CoV-2 in human milk was 23.1% between October 2020 and February 2021. After a PCR confirmed infection, SARS-CoV-2 specific IgA antibodies was stable over time and remained present up to at least 10 months in human milk. The high prevalence of antibodies in human milk might lead to passive immunity in breastfed infants and may serve as protection against COVID-19.

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