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Bench Research, Human Milk, and SARS-CoV-2

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Abbreviations:
SARS-CoV-2 - Severe Acute Respiratory Syndrome Coronavirus 2,
COVID-19 – Respiratory disease caused by SARS-CoV-2,
RT-PCR – Reverse transcription polymerase chain reaction

In this issue of *Pediatrics*, Carina Conzelmann et al. examined whether Holder pasteurization of human milk, i.e. heating to 62.5 degrees Celsius for 30 minutes, can inactivate SARS-CoV-2.[1] In the laboratory, the authors "spiked" five individual women's expressed milk samples with five different SARS-CoV-2 isolates, conducted Holder pasteurization (to 63 degrees C), and then assessed tissue culture infectious dose 50 (TCID50) by infecting susceptible cells and monitoring the cytopathic effect. Holder pasteurization effectively inactivated SARS-CoV-2, and additionally, they noted a 40.9-92.8% viral titer decrease in human milk as compared to the control medium, confirming human milk's unique antiviral properties.

This important study adds to the limited evidence that pasteurized donor human milk is safe [2], but placing it within the clinical context is key.[3] Providers and parents should not leap to any of several possible unfounded conclusions: (1) that the milk of a mother who has SARS-CoV-2 infection will be infected, (2) that her milk must be expressed to be fed to her infant, or (3) that her milk should be Holder pasteurized prior to feeding. While much remains to be learned about human milk and SARS-CoV-2 infection, preliminary laboratory and clinical reports have led to professional guidance supporting the safety of breastfeeding if the SARS-CoV-2-infected mother is well enough to care for her infant.[4-7] When she is too ill to feed directly, or her preterm infant cannot directly breastfeed, expressing her milk and feeding it to the infant is preferred.[4-7] These recommendations appropriately acknowledge the extraordinary health benefits of human milk feeding.[8-10]

In fact, preliminary evidence from laboratory[11] and clinical studies[12,13] suggests that (1) SARS-CoV-2 is unlikely to infect human milk, and (2) any particles detected in human milk are likely not to be infectious. In order for SARS-CoV-2 to enter and infect cells, two processes have to occur. SARS-CoV-2 must bind to host cells via the angiotensin-converting enzyme 2 (ACE2)

receptor and cell entry must be facilitated by host cell proteases TMPRSS2, CTSB, or CTSL. To investigate human milk susceptibility to SARS-CoV-2, Goad et al. examined whether human mammary gland luminal epithelial cells (in which milk is manufactured) express ACE2, TMPRSS2 and CTSB/L.[11] Just 5% of mammary gland cells expressed ACE2, and none of the cells co-expressed ACE2 with either TMPRRS2 or CTSB/L, which would be the essential "double unlocking" needed for viral cell entry. The authors concluded that there is essentially no risk of vertical transmission of SARS-CoV2 to the infant who is breastfeeding from an infected mother, since the virus cannot enter the "milk making machinery" of the breast.

Clinical confirmation of this laboratory-based hypothesis is challenging, since early in the pandemic mother-infant dyads were separated at birth, with human milk feeding not permitted. However, recently Chambers et al. [14] analyzed 64 human milk samples from 18 SARS-CoV-2 infected women, all but one of whom were ill, both before and after a positive test. Only one sample of the 64 had detectable SARS-CoV-2 RNA by RT-PCR. This sample, and a subset of 26 samples from 9 of the women, were tested for ability to replicate by established culture methods, and all were negative.[14] This suggests, importantly, that particle detection does not equate to infectivity, and supports Goad et al.'s preliminary findings. In a comprehensive review, the World Health Organization reported that of 46 women with COVID-19 disease whose milk was tested, 43 were negative, and 3 had particles detected by RT-PCR; one of the 3 infants tested positive for SARS-CoV2 but infant feeding practices were not reported.[5] A recent case report of a 32-week, 1614 gram preterm newborn inadvertently fed SARS-CoV-2-positive human milk who did not become infected suggests that human milk is not infectious even for preterm infants.[12] In a retrospective cross-sectional study of 45 infants born to COVID-19 positive mothers, none of the 7 premature infants who were breastfed or fed pumped human milk

developed symptoms of infection.[13] To summarize, there is more to learn, however, the preliminary evidence demonstrates that human milk is not likely to be a source of SARS-CoV-2 infection for infants, term or preterm.

Finally, while Holder pasteurization is a best practice for assuring the safety of pasteurized donor human milk for preterm infants, it is not a benign intervention with respect to its impact on the immunologically competent proteins and other components of human milk[15] and should not be undertaken lightly as a faux "preventive" measure. Most studies report that Holder pasteurization reduced secretory IgA.[15] This could jeopardize the protective effect of secretory IgA directed against SARS-CoV-2 that has been detected in milk of mothers who have COVID-19. [16,17]

In summary, the illuminating laboratory research of Dr. Conzelmann et al. offers new insights about SARS-CoV-2 best appreciated within the clinical framework of our still sparse understanding of COVID-19 and human milk.

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