Postnatal Cytomegalovirus Infection Through Human Milk in Preterm Infants

Transmission, Clinical Presentation, and Prevention

Klaus Hamprecht, MD, PhD[a,*], Rangmar Goelz, MD[b]

KEYWORDS

• Cytomegalovirus • Lactation • Native breast milk • Virus reactivation
• Short- and long-term outcome • Very low birth weight infants (VLBW)
• Virus inactivation • Ganciclovir

KEY POINTS

- Cytomegalovirus (CMV) is reactivated in the lactating breast in up to 96% of CMV seropositive mothers. The onset, the dynamics, and the end of virus shedding into breast milk are interindividually variable and describe mostly unimodal kinetics.
- As early as on day 3 postpartum infectivity of human breast milk (BM)/colostrum can be detected, and a preterm infant may be infected.
- There is a relevant entity of postnatally acquired symptomatic CMV infection and disease of preterm infants through raw BM.
- Actual data are supporting negative influence on long-term cognitive development.
- Concerning prevention, only heat inactivation eliminates virus infectivity, and short-term heat inactivation is most preservative; this can be applied effectively under routine conditions.
- Short-term heat inactivation for 5 seconds at 62°C maintains the benefits of feeding BM without the disadvantages of CMV transmission.

INTRODUCTION

Besides evident short-term benefits for the baby,[1] breast feeding is associated with improved IQ-scores and increased educational attainment 30 years later.[2] This article will focus on the dynamics of cytomegalovirus (CMV) excretion during lactation, and describe the short- and long-term risks of CMV-infection of small preterm infants, as well as options for prevention.

Both authors contributed equally.
Disclosure statement: The authors state that there is no conflict of interest.
[a] Institute of Medical Virology, University Hospital of Tuebingen, Elfriede-Aulhorn-Str 6, Tuebingen D-72076, Germany; [b] Department of Neonatology, University Children's Hospital, Calwerstr. 7, Tuebingen D-72076, Germany
* Corresponding author.
E-mail address: klaus.hamprecht@med.uni-tuebingen.de

Clin Perinatol ■ (2016) ■–■
http://dx.doi.org/10.1016/j.clp.2016.11.012 perinatology.theclinics.com

In 1967, CMV was first isolated from human breast milk (BM)[3]; thereafter, maternal CMV shedding into milk was related to perinatal infection.[4] A few years later, transmission to term infants fed raw BM was considered to be a form of natural immunization, because there was no or only minimal morbidity.[5] A neonatal exchange transfusion-related CMV infection was reported in 1979.[6] Despite the use of CMV immunoglobulin (IgG)-negative transfusions,[7] postnatal CMV infections, especially in preterm infants, persisted. This observation led the authors to prospectively investigate the role of postnatally acquired CMV infection in preterm infants through raw BM.

CYTOMEGALOVIRUS REACTIVATION DURING LACTATION

CMV, a beta-herpesvirus, persists following primary infection for lifetime in hematopoetic CD34+ precursor cells and may be reactivated by stress, transient loss of CD4+ and CD8+ T-cell immunity, interleukin (IL)-6 signaling, cell cycle arrest, or DNA-damage.[8] Interestingly, CMV is also reactivated in healthy immunocompetent seropositive women during lactation.[5] The ratio of CMV reactivation at any stage of breastfeeding during the first 3 months after birth is high (>95%) and equals nearly the maternal seroprevalence.[9,10] CMV seroprevalences in Western Europe, the United States, Canada, and Australia range from 40% to 60%, and are above 90% in South Africa, Brazil, India, Japan, and Turkey.[11] The mechanisms leading to viral shedding exclusively into BM are not understood.

DYNAMICS OF CYTOMEGALOVIRUS REACTIVATION

Maternal CMV reactivation of seropositive mothers during lactation with shedding of viral DNA and virolactia[12] can be detected already in colostrum and normally ends after about 3 months after birth. According to the authors' experience with individual kinetics of CMV reactivation in BM of more than 500 healthy breastfeeding mothers of preterm infants, the onset of viral shedding may begin with low viral load (<1000 copies/mL) and low infectivity (without detectable infected fibroblast nuclei in short-term microculture) within 10 days postpartum. Nevertheless, also early onset of viral shedding into colostrum may occur as shown in **Fig. 1** for day 3 postpartum. The onset, dynamics, and the end of virus shedding into milk are interindividually variable and describe mostly unimodal kinetics. Using overnight microculture from cell and fat-free milk whey, peak values of virolactia and viral DNA lactia coincide, varying from 10^3 to 10^6 copies of CMV DNA per milliliter of milk whey.[13]

The study of initiation of viral shedding into colostrum shows divergent results. In a report from Gambia, CMV excretion in colostrum was observed in 100% of congenitally infected infants.[14] A Japanese study of postnatal CMV infection showed, that in 7 cases of very low birthweight (VLBW) infants, the initial viral load in BM in the first week postpartum ranges between 10 and less than 1000 copies/mL CMV DNA.[15] An Italian group detected viral DNA in 31 out of 57 (54%) colostrum samples.[16]

The CMV reactivation of mothers during lactation is a local process without detection of a disseminated or compartmentalized infection in plasma, throat, or cervical swabs.[17–19] Therefore, CMV-DNA, viral late pp67-transcripts and virions can only be detected in BM cells and cell-free milk whey.[12,13,20,21]

SPECTRUM OF CELL TYPES IN BREAST MILK

The BM cells involved in CMV reactivation include CD14+ macrophages.[13] However, CMV-infected milk cells are not essential for virus transmission.[12,19] Milk cells include breast-derived cells like lactocytes, myoepithelial cells, progenitor cells, and stem