Transmission of cytomegalovirus via breast milk to the prematurely born infant: a systematic review

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Abstract

To analyse current data on transmission of human cytomegalovirus (HCMV) via breast milk with subsequent symptomatic HCMV infection of the preterm infant and to report on long-term follow-up, a systematic literature review was performed using EMBASE, MEDLINE and CINAHL (January 1966 to December 2008) Studies were included for analysis if congenital HCMV infection was excluded and transmission via breast milk was either confirmed or strongly suspected. Twenty-six studies were included for analysis. Maternal HCMV-IgG-positivity was reported to be in the range 51.6–100% (median 81.6%), HCMV-IgG detection in breast milk in the range 67–97.2% (median 80%) and HCMV-positivity of the infants in the range 5.7–58.6%. Symptomatic HCMV disease occurred in 0–34.5% (median 3.7%) and severe sepsis-like syndrome in 0–13.8% (median 0.7%). Data on long-term outcome of preterm infants with symptomatic HCMV infection revealed a low risk for mild neurological and cognitive sequelae, without hearing impairment. Recommendations for high-risk preterm infants diverged markedly. The current data report low rates of symptomatic disease after transmission of HCMV via breast milk to the preterm infant without evidence of certain long-term sequelae. The results of our review do not support a general approach, either by avoidance or pasteurization of breast milk, in high-risk preterm infants.

Keywords: Breast milk, cytomegalovirus, epidemiology, outcome, preterm infant, transmission
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Introduction

Human cytomegalovirus (HCMV) is an ubiquitous herpesvirus that persists lifelong in monocytes and granulocytes [1]. A typical sign of HCMV infection is so called 'owl's eye' inclusion bodies as a consequence of its cytopathogenic effect. HCMV is excreted in saliva, urine and genital secretions for months to years and is also found in breast milk, blood products and tissue- and organ-transplants [2]. Approximately 50% of adults are carriers of HCMV and therefore potential sources of transmission [3]. In general, postpartum HCMV infection in infants and children takes an asymptomatic course. Symptomatic congenital disease may include intrauterine growth retardation, thrombocytopaenia, prematurity, hepatosplenomegaly, 'blueberry-muffin-like' rash, pneumonia, intracranial calcifications, microcephaly, jaundice, chorioretinitis, hearing loss and psychomotor retardation [2,3]. Diagnostic methods include PCR technique, cell cultures and detection of HCMV specific antibodies or intracellular viral proteins [4,5]. Gancyclovir has proved to be effective in infants with severe symptomatic congenital infection by reducing hearing impairment during a 1-year follow-up [6].

Subsequent to the early 1970s, human breast milk has been known as a potential source of HCMV infection, and different transmission rates from the mother to the child have been reported [7]. In 17of 63 HCMV positive women (27%), HCMV was isolated from breast milk mainly within the first week postpartum (range 2 days to 10 weeks) [7]. In a cross-sectional study, HCMV-infected breast milk was suggested to be the most important source of HCMV infection during the first year of life (Stagno *et al.* 1980) [8]. In 1983, signs of neutropaenia, lymphocytosis, thrombocytopenia and symptoms of hepatosplenomegaly were associated with HCMV disease in infants infected via breast milk [9]. In 1998, high rates of very low birth weight infants were reported to be at increased risk of symptomatic HCMV infection [10].

Methods to prevent infection via breast milk in preterm infants include heating and freezing procedures. Holder pasteurization (62.5°C, 30 min) and short–term heating (72°C, 5–10 s) are referred to as the most effective methods for reducing the risk of HCMV transmission via breast milk [11–15]. Although freezing procedures do not completely eliminate the virus, these methods are found to be less harmful to immunological factors contained in breast milk. Thus, different recommendations for breastfeeding the premature born infant have been reported [16–21].

This review aims to elucidate current knowledge of HCMV transmission via breast milk and to detail the possible sequelae for the preterm infant.

Materials and Methods

The EMBASE, MEDLINE and CINAHL databases were searched systematically to identify all papers published in the English and German literature on the relationship between CMV infection transmitted via breast milk and associated sequelae, during the period January 1966 to December 2008. For the search, the following keywords were utilized both individually and in different combinations: infant-newborn (Medical Subject Headings, MeSH), OR infant-premature (MeSH), OR infant, low birth weight (MeSH), OR infant, very low birth weight (MeSH), OR Infant-preterm (MeSH), OR infant, premature (MeSH), OR infant, newborn (MeSH), OR newborn (text word), OR infant (text word), OR neonate (text word), OR premature birth (text word), cytomegalovirus (MeSH), OR epidemiology (MeSH), OR transmission (MeSH), breast (MeSH), OR breastfeeding (MeSH), OR milk, human (MeSH), OR breast milk (MeSH), OR human, milk (MeSH), OR immunologic factors (text word), OR antiviral factors (text word), outcome (MeSH), OR neurodevelopmental-outcome (MeSH), OR follow-up (MeSH).

Studies were included for analysis if congenital HCMV infection was excluded and transmission via breast milk was either confirmed or strongly suspected. Reports on less than ten infants were included and presented as case reports. A diagnosis of HCMV infection had to be confirmed by either PCR or ELISA technique for HCMV-IgM and IgG in studies. Premature birth was defined as birth before completion of 37 weeks of gestation. Transmission via breast milk had to be confirmed or strongly suspected in studies.

Data were evaluated according to the rate of transmission of HCMV from the mother to the premature born infant during lactation, seroprevalence of mothers, detection of HCMV in breast milk (rate and time of conversion during lactation), methods of HCMV detection, seroreactivity of HCMV in the infants (rate and time of detection in the newborn), risk of acquiring disease in the newborn, and symptoms and signs of the infants' disease. In addition, short-term and long-term sequelae of HCMV disease in the infants were evaluated.

Results

In total, 26 studies eligible for inclusion were identified [9,10,22–45]. Twenty studies [9,10,22–39] and four case reports [40–43] evaluated clinical manifestations of HCMV disease in the preterm infant. Five studies reported long-term sequelae of HCMV disease [29,30,34,42,44]. One study evaluated virus secretion in preterm infants [45]. Twelve studies used PCR and seven used HCMV serology for HCMV detection. Additionally, viral cultures were used in 14 out of 16 studies [10,22,23,25–27,29–31,34–37,39]. Eight studies showed data concerning the detection of HCMV in breast milk [10,22,23,25,26,28,30,37] and six studies documented the time of HCMV detection in breast milk [10,22,23,28,30,37].

All studies included were prospective [10,22,23,25–32,34–37,39]. HCMV-IgG seroprevalence of mothers was reported to be in the range 52–97%, HCMV-positivity of infants was reported to be in the range 5.7–58.6%. HCMV was detected in breast milk of 66–96% (median 87%) of HCMV-IgG positive mothers. The time of first detection of HCMV in breast milk was in the range 8–119 days. Five studies reported HCMV detection within the first 2 weeks after birth [22,23,28,30,37], one study reported HCMV detection later than 2 weeks postpartum [10], and ten studies did not report the exact time of detection. Study design, inclusion criteria, methods, rate and time of HCMV detection in breast milk and infants of 16 studies providing the required information completely or in part are summarized in Tables 1 and 2 [10,22,23,25–32,34–37,39]. The features found in HCMV-positive infants with breast milk-acquired infection included: sepsis-like symptoms, hepatopathy, hepatosplenomegaly, hepatitis, thrombocytopaenia, neutropaenia, myoclonia, petechiae, respiratory distress syndrome, hyperbilirubinaemia, bradycardia, apnoea, cholestasis, jaundice, extended bowel, grey pallor, elevation of liver enzymes, pneumonitis, lymphadenopathy, maculopapular rash.

The main features and reported frequencies in 25 studies are shown in Fig. 1.

HCMV transmission to the preterm infant varied in the range 5.6–58.6% (median 20%). The risk of symptomatic disease in the preterm infant was in the range 0–34.5% (mean 3.7%). Sepsis-like signs in preterm infants were observed in 0–13.8% (mean 0.7%); the data are summarized in Table 3.

TABLE 1. Study design and inclusion criteria of 16 studies providing data on human cytomegalovirus transmission rates via breast milk to the preterm infant [10,22,23,25–32,34–37,39]

Year	Study design	Population	GA/BW	Number of mothers	Number of infants	Study period (years)	References
1998	Prospective	Preterm infants	<32 weeks or <1500 g	56	67	1	[10]
1997	Prospective case study	Suspected disease (56%), Screening (44%)	<32 weeks or <1500 g	15	16	1.6	[22]
2001	Prospective, case–control study	Preterm infants and their mothers and matched controls	<32 weeks or <1500 g	151	170	3	[23]
2001	Prosp.	Preterm infants and their mothers	<34 weeks	24	31	0.5	[25]
2002	Prospective	Preterm infants and their mothers	<34 weeks	41	54	1	[26]
2002	Prospective	Preterm infants and their mothers	<32 weeks	38	40	1	[27]
2003	Prosp.	Preterm infants and their mothers	<34 w or <2000 g	30	43	1	[28]
2004	Prosp., case control study	Preterm infants infected via breast milk	<32 w or <1500 g	–	22	3	[29]
2004	Prosp., case control study	Breastfed preterm infants	<35 w or <1500 g	38	42	2	[30]
2004	Prosp.	Infants admitted to NICU, screened by symptoms	24-38 w 705-2220 g	–	16	5	[31]
2004	Prosp.	Preterm infants and their mothers	<34 w or <1500 g	121	127	1	[32]
2005	Prosp., case control study	Breastfed and formula fed preterm infants of HCMV+/– mothers	<32 w or <1500 g	77	96	3	[34]
2005	Prosp.	Very low birth weight preterm infants	≤1000 g	101	119	1.1	[35]
2006	Prosp., case control study	Preterm infants with HCM-viruria during hospital stay	≤30 or <1000 g	–	40 of 463 infants	8.5	[36]
2007	Prosp. case study	Preterm infants and their mothers	24 + 2 to 27 + 5 w	6	10	0.25	[37]
2008	Prosp., case control study	Preterm infants and their mothers	≤31 w	48	58	2	[39]

GA, gestational age; BW, body weight.

TABLE 2. Methods, rates and time of human cytomegalovirus detection in breast milk and the preterm infant of 16 studies [10,22,23,25–32,34–37,39]

Breast milk			Infants		
Methods	**Rate (%)**	**Time (days)**	**Methods**	**Time (days)**	**References**
PCR, culture	85	≤56	PCR, culture	≤56 (29%) >56 weeks (71%)	[10]
PCR, culture	88	8–119	PCR, culture, serology[a]	30–85	[22]
PCR, culture	93.6	10[c] (virus) 3.5[c] (DNA)	PCR, culture	28–69 (mean 42)	[23]
PCR, culture	67	–	PCR, culture	Median 34.2	[25]
PCR, culture	68	–	PCR, culture	7–83 (median 25)	[26]
–	–	–	Culture	62	[27]
PCR	87.5	≤14 (94%) >14 (6%)	PCR	28–96	[28]
PCR, culture	–	–	PCR, culture, serology[b]	23–190	[29]
PCR, culture	97.2	12.3[d] ± 9.4	Culture, serology	21–168 (mean 77)	[30]
–	–	–	Culture, serology	27–120 (median 63)	[31]
–	–	–	PCR, enzyme immunoassay	32–140 (median 75)	[32]
–	–	–	PCR, culture	21–56	[34]
-	–	–	Culture, serology	48–72	[35]
PCR, culture, serology	–	–	PCR, culture, serology	Median 45.5	[36]
PCR, culture	80	≤14	PCR, culture	34 and 46 (two cases)	[37]
–	–	–	PCR, culture, serology	43–89 (median 73)	[39]

[a]Cord and venous blood at birth.
[b]Cord blood.
[c]Median.
[d]Mean.

Five studies were excluded from the final analysis because they did not fit the inclusion criteria or contained insufficient data for final analysis. The study by Dworsky *et al.* 1983 [46] had to be excluded because data on preterm infants were not reported separately. The authors included 58 mother–infant pairs of term and preterm infants, aiming to compare rates of HCMV shedding into saliva, urine, genital secretions and breast milk in postpartum women with rates of acquisition of infection by their infants. None of the infants born to seronegative mothers became infected during the study period in contrast to 12 infants (30%) born to 41 seropositive mothers, who became infected between birth and 8 months of age. Infants who breastfed for longer than 1 month became infected more often (p 0.15). Two of 13 preterm infants (15.4%) developed symptomatic disease (pneumonitis), which resolved. Long-term sequelae such as

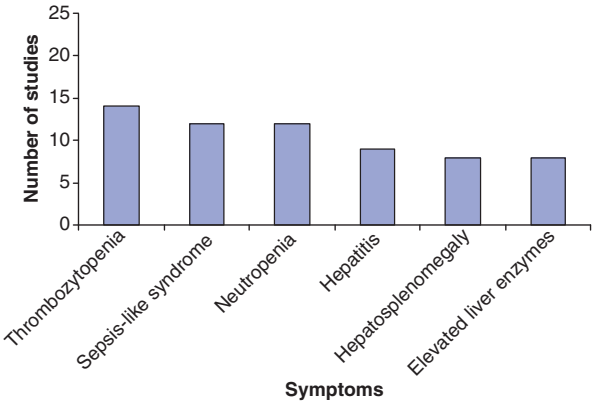

FIG. 1. Number of studies reporting on main symptoms of infants with human cytomegalovirus infection via breast [9,10,22–43].

sensoryneural hearing loss did not occur during the study period. The study by Granström *et al.* [47] was excluded because almost all the children were born at full term, and transmission via breast milk was not confirmed. Kumar *et al.* [48] reported on a low number of infants infected postnatally, and transmission via breast milk could only be assumed. In a study by Kumar *et al.* [49], no association of HCMV transmission with breastfeeding was documented and Whitley *et al.* [50] reported on formula-fed infants acquiring HCMV in early infancy.

Long-term outcome

Five studies reported on long-term outcome of HCMV infection transmitted via breast milk in preterm infants [8,29,30,34,44].

Chronic excretion of HCMV in urine and saliva was found to persist in infected infants for over 2 years [8,29]. By contrast to congenital HCMV infection, no association with sensoryneural hearing loss has been documented [29,30,34,44]. Regarding neurological status, motor development and development of speech, no significant differences were found between HCMV-infected infants and controls [29,30,34]. Only one study reported severe neurological sequelae in infants with perinatally acquired HCMV infection and onset of excretion during the first 2 months of life [44]. Later HCMV acquisition was not associated with neurological sequelae. However, the number of infants who acquired HCMV via breast milk was not clearly defined.

The following studies did not match the inclusion criteria but provide additional information on early postnatally acquired HCMV infection. In 13 of 46 HCMV positive infants (28.3%), who were followed-up at 2 years of age, a poor performance of speech (Denver Development Screening Test) and, in two children (4.4%), a mild developmental retardation were observed (Granström 1979 [47]). Tests regarding gross and fine motor skills did not show any significant differences from healthy infants. Ten infants with postnatally acquired HCMV infection were followed-up at 4.5–10.7 years of age by Kumar *et al.* 1984 [48]. The mean WISC-R intelligence quotient (Weschler Intelligence Scales for Children) for postnatally infected infants was 89.0 and correlated well with maternal IQ (84.5). No hearing abnormalities were found. In another study by Kumar *et al.* 1984 [49] 21 infants with postnatally acquired HCMV infection, who were followed during the first 12 months of life, showed a mean IQ of 107, which did not differ significantly from that of non-infected controls (IQ 102). Neither study provided information on prematurity. The study by Peckham *et al.* 1987 [45] revealed virus secretion up to 36 months of age without data on neurodevelopmental outcome of the children.

TABLE 3. Data from 12 studies reporting on human cytomegalovirus (HCMV) seropositive mothers, number (%) of HCMV positive infants, number (%) of infants with symptomatic and severe disease (sepsis-like syndrome) [10,23,25–28,30,32,34,35,37,39]

Mother HCMV+	Breastfed infants	HCMV+ infants	%	Symptomatic infants	%	Severe disease	%	References
29	29	17	58.6	10	34.5	4	13.8	[10]
78	87	33	37.9	16	18.4	4	4.6	[23]
24	20	5	25	0	0	0	0	[25]
41	33	13	39.4	3	23.1	1	7.7	[26]
28	18	1	5.6	0	0	0	0	[27]
24	30	3	10	0	0	0	0	[28]
36	40	6	15	5	12.5	5	12.5	[30]
121	49	13	26.5	0	0	0	0	[32]
72	70	4	5.7	1	1.4	1	1.4	[34]
56	61	4	6.6	1	1.6	1	1.6	[35]
5	7	2	28.6	1	14.3	0	0	[37]
29	35	5	14.3	2	5.7	0	0	[39]
Mean (median)			22.8 (20)		9.3 (3.7)		3.5 (0.7)	

HCMV+, HCMV positive.

Discussion

The present review has revealed HCMV transmission via breast milk in 66–96% of HCMV-IgG positive mothers with subsequent HCMV-positivity of the infants in the range 5.7–58.6%. Median rates of symptomatic HCMV disease were 3.7% in HCMV positive infants, with rates of 0.7% for severe sepsis-like syndrome. Rates of infection and disease vary greatly from study to study, probably reflecting differences in study design, different incidence rates of HCMV positive mothers and different inclusion criteria for preterm infants according to either gestational age or birth weight (e.g. preterm infants below 32 or 34 weeks or up to 38 weeks of gestation or infants below 1000 or 1500 g), highlighting the urgent need for a prospective multicentre study to address these questions. According to the few data concerning long-term outcome in preterm infants with overt HCMV infection, a low risk of mild neurological and cognitive sequelae without hearing impairment was suggested.

Symptomatic HCMV infection via breast milk does not usually occur in full-term infants because of the transmission of protective maternal antibodies, starting within the 29th gestational week [19,51]. In very premature born infants, this transmission of maternal antibodies is missing, which puts them at high risk for symptomatic HCMV infection transmitted via breast milk [51,52]. Low birth weight and an early postnatal transmission are risk factors for symptomatic and even severe infection [18,53]. HCMV transmission via human milk might be a cofactor aggravating the clinical course of pre-existing pulmonary, haematological or hepatic conditions in certain preterm infants, although it is unlikely to cause symptoms in healthy preterm infants [38,54]. However, primary HCMV infection even creates the possibility of HCMV pneumonitis in full-term born infants [51]. Sequelae of HCMV infection transmitted via breast milk within the first 2 months of life are difficult to separate from complications of premature birth [19]. Data on long-term sequelae are scarce, suggesting no sensoryneural hearing loss and only minor effects on neuromotor development [18,51].

Pasteurization is very effective in inactivating HCMV in breast milk, but also decreases the protective factors in breast milk [18,19,51]. Freezing procedures preserve the protective factors but are not effective in inactivating HCMV [18,19,51]. However, breast milk has several advantages and possibly provides long-term protection [19,20,55]. The issues raised by Willeitner in 2004 [54] regarding whether mothers of infants at risk who intend to breastfeed should be tested for HCMV-IgG status and whether the disadvantages of pasteurization outweigh the risks of contracting HCMV are still debated.

There is little consensus among paediatricians and neonatologists on the approach to the prevention and management of HCMV infection acquired via breast milk in preterm infants. The issue has been raised by a series of reports from investigators in Tübingen, Germany, as reported in detail by Schleiss [56] Currently, there are few national recommendations on handling the breast milk of HCMV-IgG positive mothers. The American Academy of Pediatrics [17] recommends human milk for preterm and other high-risk infants either by direct breastfeeding or using the mothers own expressed milk. Banked pasteurized human milk is suggested to be a suitable feeding alternative. Decisions about breastfeeding of very low birth weight infants by mothers known to be HCMV-seropositive should be made with caution, weighing the potential benefits of human milk versus the risk of HCMV transmission. The Committee for Nutrition of the Austrian Society of Paediatrics and Adolescent Medicine [16] recommends determining the HCMV serostatus of every mother and, in the case of HCMV-IgG-positivity, the colostrum has to be abandoned and breast milk has to be pasteurized before being fed. This procedure is suggested for the infant up to the corrected gestational age of 35 weeks. The French Society for the Safety of Nutrition [18] restricts the feeding of raw breast milk to preterm infants above 32 weeks of gestation (above 1500 g). The guidelines of the Swedish National Board of Health and Welfare recommend the freezing of HCMV positive maternal milk for preterm babies <32 weeks of gestation [57].

Interestingly, approximately 30 years ago, Stagno *et al.* [8] and, more recently, Stronati *et al.* [58] summarized this mode of HCMV transmission via breastfeeding as a form of passive/active immunization. In most cases, the infection occurs in the presence of specific anti-CMV antibodies and despite the presence of immunoglobulins, macrophages, neutrophils and lymphocytes in breast milk, which should ensure both a specific and a nonspecific antiviral defence. In view of the biological and nutritional value of breastfeeding, this transmission route should be interpreted as a positive factor [58]. Three decades later, we still share the view of Stagno *et al.* [8] that the minimal risk associated with the transmission of HCMV through breast milk is clearly outweighed by the well-established value of breastfeeding.

Summarizing the results of our review, the mean rate of HCMV transmission was 22.8%, the mean risk of symptomatic disease was 3.7%, and that of sepsis-like symptoms was 0.7%. The question remaining is whether the low risk of severe symptomatic disease justifies withholding colostrum and breast milk feeding from all preterm infants below 32 weeks of gestation. Do we trade the benefits of human

milk for the slight chance of 'clinical deterioration' [59]? In our opinion, an individual decision, based on the health status of the preterm infant, should be preferred to a general approach.

Transparency Declaration

The authors declare that there are no conflicts of interest.

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