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Breast milk-acquired cytomegalovirus infection in very low birth weight infants

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Abstract

Perinatal transmission of human cytomegalovirus (HCMV) infection in very low birth weight (VLBW) premature infants can lead to serious clinical symptoms and it has been increasingly recognized that breast milk is the most frequent route of transmission. Breast milk is considered ideal food for newborns because of its nutritional value and anti-infectious components, but it can also be vehicle for viral and bacterial infection. The majority of HCMV seropositive mothers shed the virus into their breast milk and can transmit infection to their offspring. Perinatally acquired infections in full-term neonates are usually asymptomatic without sequelae due to protective maternal HCMV-specific antibodies received during pregnancy. In contrast, VLBW preterm infants are at risk of symptomatic infection with neutropaenia, thrombocytopaenia, sepsis-like syndrome and, less frequently, pneumonia and enteric infection. Postnatally acquired infection seems to spontaneously resolve without altering the clinical outcome. Ganciclovir treatment is restricted to severe symptomatic infections. Preterm infants with a gestational age <30 weeks, or with a

birth weight <1000 g, are at greater risk of severe postnatal symptomatic HCMV infection, transmitted via maternal milk. The pasteurization of breast milk entirely eliminates infectivity and prevents virus transmission but alters nutritional and immunological milk properties, and freezing reduces, but does not eradicate, infectivity. Most authors encourage fresh maternal breastfeeding because its beneficial effects outweigh the risk of a transient infection, sequelae-free. Nevertheless, an individual decision based on the condition of health of the infant is important.

Keywords:: HCMV postnatal infection, preterm infants, HCMV postnatal transmission, breastfeeding

Introduction

The human cytomegalovirus (HCMV) is the cause of the most common congenital and postnatal viral infections worldwide. The frequency of congenital infection is 1% of all live-born infants and it known that neurosensorineural hearing loss and mental retardation are the most common sequelae.

Conversely, postnatal HCMV infection has not been broadly investigated in the past, probably because it is often asymptomatic and thought to result in low morbidity. Nevertheless, after the 1990s, studies reported that postnatal infection in premature infants can lead to serious clinical symptoms, including respiratory compromise, neutropaenia, thrombocytopaenia, hepatomegaly and sepsis-like syndrome. As a result, there is renewed interest in the effects of HCMV infection acquired during the immediate postnatal period.

Postnatal infection can be acquired through transfused blood during the birthing process, due to infected cervical secretion, and through breast milk. The shedding of HCMV into breast milk represents the main source of postnatal infections during the first year of life [1-5]. Maternal breast milk is the recognized feeding method of choice for infants, even for preterm newborns, with balanced nutrients and a large array of anti-infectious components,

nevertheless most seropositive women shed HCMV into their breast milk with a consequent transmission rate of 40% of the virus in the breast-fed infants.

Perinatal acquired infections in full-term neonate, due to the protective maternal HCMV-specific antibodies received during pregnancy, are usually asymptomatic and without sequelae. In contrast, very low birth weight (VLBW) preterm infants are at risk of infection, even with severe symptoms, due to an HCMV infection transmitted via breast milk.

For this reason, various interventions have been proposed to inactivate HCMV in breast milk, by means of heating (the most efficient method) or freezing and thawing. All these methods alter milk properties and, therefore, continuing natural breastfeeding for its beneficial effects is also recommended [6–10].

Nowadays there is no consensus on the matter, but various recommendations for breastfeeding premature infants, particularly preterm newborns with a gestational age of < 30 weeks or <1000 g body weight, have been given in some National guidelines (France, Austria) [11].

Literature reports a wide range of data on the rate of breast milk-acquired HCMV infection (5.7–58.6%) which depends on the study design and on the treatment of the milk [7, 12, 13].

The aim of this article is to review recent literature about the breast milk-acquired HCMV infection in VLBW infants, considering the rate of transmission, clinical symptoms and prevention measures. Therapeutic options for symptomatic infections and/or long-term sequelae have also been reviewed.

HCMV in breast milk

HCMV is a ubiquitous virus of the herpes virus family. The worldwide seroprevalence range in adults is 52–97% and the

higher seroprevalence may be attributable to lower socio-economic and crowded or unsanitary living conditions.

Seropositive mothers can suffer an HCMV reactivation with shedding of the viable virus, or may have the HCMV-DNA present in breast milk after delivery.

The exact mechanism is not known, but there is evidence of reactivation of the mammary gland, allowing for the subsequent shedding of the virus during lactation, with no evidence of systemic reactivation, symptoms or increasing laboratory indices (negative serum HCMV-IgM, negative viruria) [6].

In 1967, Diosi et al. were the first to report the isolation of HCMV in human milk. Subsequently other studies referred to the presence of the virus in breast milk from seropositive mothers with an increased virus shedding rate into breast milk ranging from 42% to 97%, even up to 100%. Conversely, when the mother was seronegative, no evidence of viral shedding was reported [1, 12, 14].

The increased detection of HCMV depends on a highly developed technique: the virus culture in unseparated milk, the polymerase chain reaction (PCR) technique and separation procedures in cells and fat-free milk whey fraction.

Viral DNA isolation in milk (DNA lactia) by PCR is more sensitive, precocious and stable in terms of time analysis than culture for virolactia (presence of infectious virus in milk) [1, 5, 12].

Milk serum (whey) is the material of choice for detecting CMV in breast milk because it enables the cell-free virus to be detected. This procedure, as in the case of viral isolation in culture, proves less sensitive if applied to whole milk or to separated milk fraction [15]. HCMV DNA in milk whey is the most reliable parameter for detecting maternal viral reactivation during all stages of lactation. Nowadays, it is recognized that the incidence of CMV DNA in breast milk

equals the maternal seroprevalence, whereas the positive concordance between the infectious virus presence in the milk (possibly significant in the infection transmission) and CMV DNA is variable, ranging from 17% to 85% [16].

Maternal HCMV reactivation during lactation is described by unimodal kinetics and is a self-limited process. HCMV secretion into milk may begin in the first week post partum with a low viral load and reaches a maximum peak at about 4–8 weeks after birth, ending with a decline of virus secretion around week 9–12 postpartum [14, 17, 18].

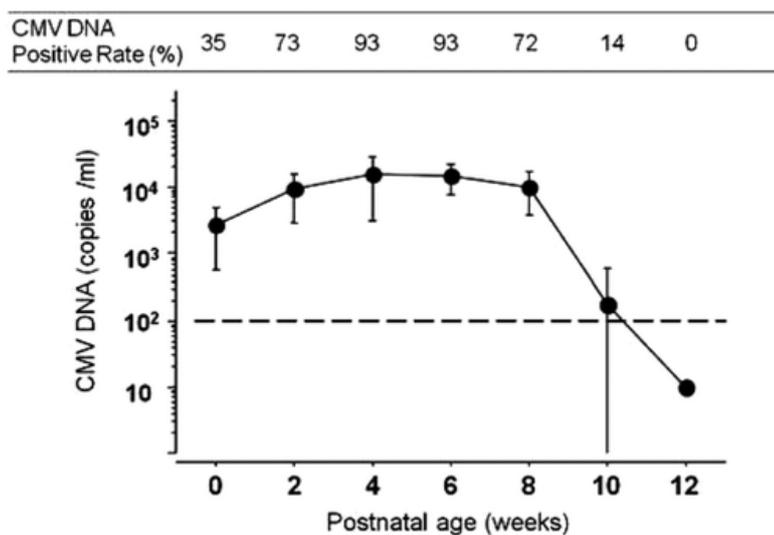
Hamprecht et al.'s study of 151 mothers and their 176 preterm infants (gestational age < 32 weeks or birth weight < 1500 g) found that viral reactivation in seropositive mothers was 96% (73 of 76). The cumulative rate of transmission was 37% (27 of 73 mothers; 33 infants). Chiavarini et al. found 54.4% of positive colostrum samples, and most of the samples (63.5%) become positive at a later stage [9, 12].

In a study of 25 mothers and 27 preterm infants with a gestational age < 28 weeks or birth weight < 1000 g, Hayashi et al. confirmed the previously demonstrated viral kinetics and found a detectable HCMV DNA in 100% of breast milk from seropositive mothers, while HCMV DNA was not detected at all in breast milk from seronegative women. In total, 7 out of 20 colostrum samples (35%) contained HCMV DNA. At 2 weeks postpartum, the HCMV DNA copy number increased and it peaked at 4–6 weeks postpartum. CMV DNA shedding in breast milk continued until 8 week postpartum, and at 10 weeks, viral DNA was only detected in 1 sample. Finally, at 12 weeks, HCMV DNA was not detected in any of the samples.

The authors confirmed that maternal viral reactivation does not depend on gestational age at delivery, and CMV reactivation during lactation begins 1–2 weeks postpartum and ends before 10 weeks postpartum (Figure 1) [14].

Figure 1. by Hayashi et al. 2011: Kinetics of cytomegalovirus (CMV) DNA copy number in breast milk. The mean CMV DNA

copy numbers in all colostrum samples as well as the breast milk of 21 CMV-seropositive mothers are reported above. The CMV DNA copy number was measured by real-time PCR. DNA copy numbers in colostrum are shown at 0 weeks postnatal age. Mean copy numbers of CMV DNA are represented by the black dots; error bars indicate 95% confidence intervals. The dotted line represents the detection limit of the assay [14]. Reprinted by permission from Macmillan Publishers LTD: J. Perinatol, 2011; 31: 440-445, copyright 2012.



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Chiavarini et al. demonstrated that the highest values of HCMV DNA copies in breast milk, ranging between 10^4 and 10^6 copies/ml, were detected from 4 to 6 weeks postpartum [12].

Nevertheless, the duration of the virus in breast milk varies greatly. Vochem et al. demonstrated that the mean period of HCMV virolactia is 7.6 weeks, but positive viral cultures have been reported from the first day up to 9 months postpartum [17].

Transmission of the infection

Stagno reported that nearly 40% of all seropositive mothers,

who have been breastfeeding for at least 1 month, transmit the infection to their infants [1].

The aforementioned data is different for preterm infants: the mean rate of HCMV transmission is from 5.7% to 58.6% and this probably reflects the different types of breastfeeding and milk preservation [7].

It is known that heating techniques or freezing at -20°C significantly removes or reduces the HCMV viral load in breast milk and the risk of infection as a result, but does not completely eliminate it.

The highest incidence of transmission, from 37% to 59% is reported when maternal milk is given fresh or preserved at $4-8^{\circ}\text{C}$, while the lowest transmission values, from 2.5% to 25%, were found referring to the use of frozen milk [7, 18].

In the previously cited study by Hamprecht et al., conducted on 176 preterm infants (gestational age < 32 weeks or birth weight < 1500 g), 73/76 (93%) 37% of HCMV seropositive mothers transmitted the infection to their respective offspring (27/73 mothers, corresponding to 33 babies) as a result of fresh milk breastfeeding [3].

Croly-Laburdette et al. found that HCMV was transmitted, via fresh or pasteurized breast milk, to preterm infants of a gestational age < 33 weeks, in 14.3% of cases. The authors studied the babies until 2 months of age [19].

Doctor et al. reported a 6.2% incidence of HCMV transmission in preterm infants born with a birth weight < 1000 g, breast fed using stored milk at 4°C for 24 hours or freeze-stored at -20°C for up to 3 months [20].

Jim et al. observed a 15% HCMV transmission when preterm infants (< 35 weeks) were exclusively breast fed by freezing breast milk at -18°C overnight or for several days [21], while Hayashi et al. measured an HCMV transmission of 4.3% (1 out of 22 preterm infants) when frozen/thawed breast milk is predominantly used [14]. Chiavarini et al.

observed HCMV transmission in only 1 out of 47 (2.5%) preterm infants breast fed using milk frozen for 72 hours before thawing [12].

The detection of HCMV DNA in breast milk is sufficient to transmit the infection to offspring, although the proportion of virolactia is higher in transmitter than nontransmitter mothers (96 vs 70%). Capretti et al. reported that 21 out of 53 seropositive mothers who reported positive virolactia were shedding the virus in breast milk and transmitting the infection (incidence of 35%) to their preterm newborns (fed exclusively using raw milk, gestational age < 32 weeks or birth weight < 1500 g), while none of the infants fed with breast milk without virolactia was infected [16]. HCMV infection can be observed at an early stage, before 2 months of life, but can also be observed after 3 months, and early gestational age at birth seems to cause symptomatic and severe infections. Nevertheless, with regard to the virus kinetics, as the incubation time of the HCMV infection is between 30 and 120 days, mother-to-infant infection, transmitted via breast milk, should not occur until at least 6 weeks after the delivery, as Chiavarini et al. observed [12]. Jim et al. reported the onset of viruria at a median age of 73 days [21] and Buxmann et al. at a median age of 63 days postpartum [18].

The high rate of HCMV reactivation in the breast milk of seropositive breastfeeding mothers and the early onset of DNA in breast milk, as well as the duration of lactation, all result as potential risk factors for infecting the infant with HCMV.

Transmission normally coincides with the proximity of maximum level of viral DNA lactia or virolactia, and is related to a low gestational age at birth [8, 9, 16, 23]. van der Strate et al. demonstrated that the viral load in the transmitter breastfeeding mothers was higher than the nontransmitter group. They concluded that HCMV transmission to the newborns was only observed above a viral load of about 7×10^3 Genomes/ml [24]. In a study of

17 seropositive mothers, Jim et al. reported that the median viral load in breast milk from mothers of infected infants was significantly higher than the load from mothers of noninfected infants at 4 weeks postpartum. HCMV was detectable in breast milk for a significantly longer period of time in the mothers of infected infants (7.5 vs 2.6 weeks) [22].

Preterm birth is an independent risk factor for HCMV transmission probably due to a reduced transplacental transfer of antibodies prior to 28 weeks of gestation. The risk of infection significantly decreased for each additional week of gestation with a lower gestational age (30%) and ethnicity was found to be a strong risk factor. The risk of infection was nine times higher in infants born from nonnative mothers than native (Dutch) mothers, possibly because of differences in the seroprevalence [2].

In contrast with other authors, Capretti et al. did not identify the low gestational age as a risk factor because their policy for prevention of nosocomial infections in VLBW infants included the administration of IgM (IVIGMA) to infants born before 28 weeks of pregnancy during the first 3 days of life [16]. Finally, the administration of raw milk is an important risk factor because pasteurization or frozen/thawed milk can effectively decrease the milk viral load.

Buxmann et al. observed that seropositive mothers of preterm infants (gestational age <31 weeks) who transmitted the infection to their children had significantly higher HCMV-IgG levels than the mothers of noninfected children, and these high levels could be an indicator of subclinical maternal reactivation that can lead to transmission [18]. In a subsequent study, Jim et al. reported contrasting data and the conclusions require further evaluation due to the small number of patients [22].

Clinical symptoms of HCMV infection

Postnatal infection acquired via breast milk appears to be largely asymptomatic without long-term sequelae in full-term infants. Stagno et al. conversely reported that acute problems seem to be limited to lower respiratory disease in some of these infants. Nevertheless, HCMV was found to be the etiologic agent responsible for pneumonia in 20% of the patients aged from 2 to 12 weeks in a study of perinatally acquired infection [1, 25].

In preterm newborns, the infection acquired via breast milk is often asymptomatic in the majority of cases (>50%), but literature has found that postnatal infection in premature infants can cause clinical symptoms, even of a severe nature. The immaturity of the immune system and reduced transplacental transfer of maternal HCMV IgG antibodies prior to 28 weeks of gestation are both responsible factors for a higher risk of severe infection in preterm newborns with a gestational age <30 weeks or <1000 g body weight at birth [9, 26]. In fact, low birth weight and early postnatal virus transmission seemed to be important risk factors for symptomatic infection [7].

Symptomatic HCMV infection can be described by various features: a transient inflammatory syndrome with leukopaenia, thrombocytopaenia and an increase of C-reactive protein, cholestasis, hepatitis with hepatosplenomegaly, alteration of liver enzymes or manifested severe clinical symptoms of a septic type (sepsis-like syndrome), it consists of apnoea, bradycardia, grey pallor of the skin, abdominal bloating and severe apnoea attacks that may require positive pressure ventilation [2, 23, 27].

The first diagnosis of a postnatally acquired infection is an HCMV-positive PCR result, viral plasma or leukoDNAemia, followed by viruria and simultaneous IgM seroconversion; the presence of virus in urine and saliva can be detected after 2 weeks. The duration of HCMV shedding in biological fluid is about 2 years. Symptomatic HCMV disease occurred in 0–34.5% (median 3.7%) and severe manifestations

occurred in 0–13.8% (median 0.7%) of preterm infected infants [7, 17].

Screening 151 mothers and their 176 preterm infants (gestational age at birth <32 weeks or birth weight <1500 g), Hamprecht et al. found that the proportion of HCMV reactivation in seropositive breastfeeding mothers was 96% (73 of 76 seropositive). The cumulative rate of transmission was 37% (27 out of 73 mothers; 33 infants). 17 (52%) of the 33 preterm infants of 27 transmitting mothers were infected without symptoms, but 16 were found to have symptomatic infections. The most common symptom was neutropaenia (<1500 cell/ μ l) and 4 infants with gestational age <26 weeks (25% of infected and 12% of symptomatic) developed sepsis-like symptoms [3].

For a period of 8.5 years, Neuberger et al. monitored 40 postnatally infected preterm infants (gestational age at birth <32 weeks or birth weight <1500 g) and a noninfected control group. The infected infants reported lower minimal platelet ($p < 0.05$) and neutrophil counts ($p < 0.001$) and a higher frequency of C-reactive protein ($p < 0.001$) increases to 10–20 mg/l than their corresponding controls. However, no association of HCMV infection with bronchopulmonary dysplasia, necrotizing enterocolitis, IVH, PVL, or ROP > grade 2 was observed. There were also no differences in gestational age, duration of mechanical ventilation, oxygen administration, or hospital stay, weight, or head circumference upon discharge. Cholestasis occurred in 4 infants from the infected group, but disappeared within 10 weeks.

These findings suggest that HCMV transmission through human milk may be a co-actor that aggravates the clinical course of pre-existing pulmonary, haematologic, or hepatic conditions in selected preterm infants, but is unlikely to cause symptoms in otherwise healthy preterm infants [28].

In their study, Capretti et al. confirmed that HCMV infection acquired through maternal milk was asymptomatic in well

growing, stable VLBW infants without chronic illness, but it can trigger a deterioration of the clinical course of a pre-existing disease, such as chronic lung disease [16].

This has initiated a discussion on gastrointestinal symptoms as it does not appear to be a recognized manifestation of postnatal HCMV infection and diagnosis is likely to be difficult. Cheong et al. identified 16 infants (0.57% of all admissions) with postnatal HCMV infection over a 5-year period. The infants had a median age of 25 weeks and median birth weight of 801 g. All infants received fresh breast milk before the onset of symptoms that ranged from minor and transient to severe and life threatening. It was, therefore, suggested that a diagnosis of "atypical necrotizing enterocolitis" or diarrhoea, abdominal distension, abdominal tenderness, and the passage of blood-stained stools in the

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preterm baby [29].

A case of a preterm twin (gestational age of 29 weeks) who was breast fed with raw milk and had postnatal-acquired HCMV infection (viruria) and evidence of necrotizing enterocolitis, but a negative bacterial culture, at the age of 6 weeks of life was observed by Gessler et al. At 70 days of life, an abdominal radiograph demonstrated distended bowel loops requiring laparotomy. Pathology findings showed ulcerating and granulating inflammation of the colonic mucosa and immunohistochemical investigations found HCMV in detached endothelial cells [30].

Two further cases have been reported from seropositive mothers who were breastfeeding their offspring. One case of HCMV enteritis involved a 2.2 kg newborn who presented NEC and subsequently developed a colonic stricture during acute illness requiring surgery. The second case was of an infant with post-necrotizing enterocolitis stenosis, which was resolved with operative measures. Histological findings of HCMV were found in the resected colon. The patients were suffering from chorioretinitis and an antiviral drug,

ganciclovir, was administered for 2 and 6 weeks respectively due to the severe symptoms [31, 32].

Altered cranial ultrasound (cUS) findings are included among clinical manifestations. Nijman et al. used the cUS to evaluate the presence and evolution, at birth and on a weekly basis until a term equivalent age, of postnatally acquired HCMV infection with lenticulostriate vasculopathy (LSV), germinolytic cysts and subependymal pseudocysts in 315 infants born <32 weeks of gestation. The authors compared the results of the corresponding infected and noninfected patients. 39 of the 315 infants were diagnosed with a postnatal infection. The majority of HCMV-infected infants (33/39, 85%) did not develop any symptoms. LSV was significantly more frequent at the full-term equivalent age in infants with HCMV infection (33% vs 11%). LSV could be the result of a necrotizing inflammation of the lenticulostriate arteries during infection and a relationship between LSV and sensorineural hearing loss in a small group of infants with congenital HCMV infection has also been observed. The 2 groups studied did not differ in any other altered cUS findings [2].

Treatment prospects and sequelae

There is little data available on the effectiveness of antiviral therapy in infants with postnatal-acquired HCMV and only individual cases have been reported.

Ganciclovir (GCV), administered intravenously is the most frequently used medicinal product, at the average dose of 12 mg/kg twice daily for no less than 2 weeks and for 4–6 weeks in the event of persistent symptoms. GCV has been administered for cases of sepsis-like syndrome and multiple organ involvement, notably hepatitis and pneumonitis, and severe diarrhoea without adverse effects or relapse, thereby shortening the course of the illness. Nevertheless, postnatal HCMV infection in the newborn generally resolves spontaneously without antiviral treatment [33].

No data has been reported on the use of oral valganciclovir, a GCV prodrug, for postnatal HCMV-acquired infection in infants and further studies are required to investigate the efficacy of HCMV-hyper-immune IVIG to prevent HCMV infection via maternal milk, also in extremely low birth weight infants, despite the fact that a reduced rate of infection has been observed in preterm treated infants <28 gestational age [16].

Congenital HCMV infection is the leading infectious cause of sensorineural sequelae in infancy (25%). As a result, preterm infants who acquire the HCMV infection via breast milk postnatally may be similar to foetuses that are congenitally infected in the intrauterine period. In fact, it is difficult to distinguish between sequelae as a result of a postnatally acquired infection via HCMV-positive breast milk and complications associated with preterm birth.

There is little information on the long-term sequelae of early postnatally acquired HCMV infection in preterm infants.

A study had discussed the neurological sequelae which were detectable at 3 years of age in a population of 23 preterm infants who acquired the HCMV infection in the first 2 months of life. The neurological sequelae were mild-moderate in 13% of cases and severe in 9% of cases [7, 34].

Vollmer et al. investigated a group of 22 preterm infants (median birth weight: 1020g, median gestational age: 27.6 weeks) with early postnatally acquired HCMV infection from breastfeeding compared to 22 HCMV-negative preterm infants who were individually matched in terms of gestational age, birth weight, gender, intracranial haemorrhage and duration of ventilation. At 2 to 4.5 years of age, follow-up assessments, consisting of a neurological examination, neurodevelopmental assessment and audiological tests, demonstrated that there was no difference between the groups with regard to neurological factors, speech and language or motor development and none of the children suffered from sensorineural hearing

loss [35].

With regard to neurological sequelae, Miron et al. observed normal hearing and development at a routine 24-month follow-up visits in the group of perinatally HCMV-infected preterm newborns [36]. Jim et al. observed that neurodevelopmental outcome did not significantly differ between the infected and noninfected group infants breast fed by HCMV DNA-positive maternal milk [21].

Preventive measures

HCMV is a labile virus and its infectivity can be reduced or eliminated by low or high temperatures. The objective is to ideally eliminate HCMV from breast milk, while conserving its nutritional and immunological properties [9].

Data contained in scientific literature reported the persistence of viral infectivity after storing breast milk at 4°C for 24 hours, while breast milk storage at -20°C for 12 hours significantly reduces the infectivity of HCMV by 90% and for 72 hours reduces the infectivity by 99% (Capretti et al. reported 75%) [16], the total elimination of infectivity (100%) is achieved by storing the breast milk for 7 days or longer and, as a result, this procedure has been recommended for breastfeeding preterm neonates [37-41].

In 18 preterm newborns (gestational age <32 weeks), Sharland et al. observed that routine freezing of breast milk from seropositive mothers at -20°C for more than 72 hours resulted in only one asymptomatic infected newborn. Freezing procedures seemed to reduce, but not fully inactivate, the infectivity of HCMV in breast milk. Freezing procedures are also able to decrease the severity of symptoms [42, 43].

An HCMV-positive culture was found in breast milk stored at -20°C for 10 days, a postnatal infection was found in 2-

month frozen milk and infectivity was also observed in milk that was frozen -20°C , and then frozen/thawed 3 times [38].

Hamprecht et al. reported that freeze-storing breast milk was not able to fully destroy viral infectivity, especially during peak levels of virus excretion into milk. Freezing is able to significantly reduce infectivity depending on the viral load. More specifically, at the beginning and at the end of viral reactivation during lactation, freezing results in the total inactivation of a low viral load [39,40].

Cryoinactivation preserves nutritional and protective factors in breast milk, such as alkaline phosphatase and lipase enzyme activities, sIgA levels, lysozyme activity and IgA [39].

It has been known for some time now that Holder or 'long-term' pasteurization (62.5°C for 30 min.) is able to completely inactivate infectivity despite the extent of the viral load. An analogous result is achieved through a 'short-term' pasteurization technique (72°C for 5 sec) developed by Hamprecht et al. [9,39]. Both techniques do not reduce detection of HCMV DNA by PCR in milk, although viral replication is not active, but nutritional and immunologic components of breast milk decrease, alkaline phosphatase and lipase activity are inactivated, and sIgA and lysozyme levels decrease [39,40,44]. As a result, pasteurizing maternal milk is not recommended and freezing/thawing human milk stored in a bank is suggested as a suitable feeding alternative preserving method.

Conclusions

On the basis of the data analyzed, breastfeeding clearly emerges as an effective mechanism of the postnatal transmission of HCMV. In actual fact, almost half of all babies breast fed for at least a month by seropositive mothers are infected in the first 6 months of life. This mode of

transmission is a form of passive/active immunization in the sense that, in most cases, the infection occurs in the presence of specific anti-HCMV 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. The infection is almost always devoid of consequences and, therefore, in view of the biological and nutritional value of breastfeeding, this transmission route should be seen as a positive factor.

With regard to the perinatally acquired HCMV infection, the number of seronegative women of childbearing age is lower and the possibility of giving birth to neonates with congenital HCMV infection is also lower as a result, as women who contract a primary HCMV infection during pregnancy transmit the infection to the foetus in 40% of cases, as opposed to only 1% in those presenting a recurrent infection [7, 37].

In accordance with international scientific recommendations, breastfeeding of term neonates should be encouraged and supported. With regard to preterm neonates, particularly those below 30 weeks of gestational age and/or below 1000 g birth weight, there is no generally accepted consensus of opinion in scientific literature.

The concern about potential short and long-term sequelae of postnatally acquired HCMV infection via breast milk in preterm infants induced the Austrian Society of Paediatrics and Adolescent Medicine to recommend determining the HCMV serostatus of all mothers. With regard to HCMV-IgG-positivity, the colostrum has to be abandoned and breast milk needs to be pasteurized before being used for feeding. This procedure is advised for infants up to the corrected gestational age of 35 weeks. The guidelines issued by the Swedish National Board of Health and Welfare recommend freezing HCMV positive maternal milk for preterm babies <32 weeks of gestation. The American Academy of Pediatrics is not conclusive and recommends human milk for preterm infants. Pasteurization and freezing procedures may reduce

infectivity of milk, but decisions regarding breastfeeding for VLBW infants by mothers known to be HCMV seropositive should be made with caution, weighing the potential benefits of human milk with the risk of HCMV transmission [11].

Feeding preterm infants with formula milk is not recommended by any guidelines (higher risk of developing necrotizing enterocolitis, infection and retinopathy of the preterm) and for most authors, breastfeeding seems appropriate for preterm newborns. In fact,

HCMV transmission via human milk is unlikely to cause severe symptomatic infections (0.7% sepsis-like syndrome) in infected infants and there is very little data on long-term sequelae, suggesting mild neurological and cognitive sequelae and no sensorineural hearing loss [7].

Nowadays, the suggestion of feeding preterm newborns with pasteurized milk only seems to exceed the potential "clinical deterioration" against the advantage of fresh milk feeding [7]. Nevertheless, further investigation is required and an individual decision based on the condition of health of the preterm infant is preferred. Nowadays, parents should be informed about the risk of their preterm infants acquiring HCMV via breast milk, fresh or frozen, in order to give their informed consent [7].

Some questions have still not been answered:

- If there is an insufficient amount of fresh maternal milk, thus requiring it to be integrated with formula milk, what is the risk-benefit ratio of infection without providing the beneficial effects of breastfeeding only [18]?
- Is it known that sepsis aggravates the clinical outcome of a preterm infant, and therefore a symptomatic HCMV transmission may be a co-factor that worsens the clinical course [8]?
- Literature reports that the majority of postnatally HCMV infected term and preterm infants do not develop long-term

sequelae; however Nijman et al. observed altered cranial ultrasound findings (LVS) in preterm newborns with postnatally acquired HCMV infection. Does the potential relationship of these findings with a possible neurodevelopmental alteration in the infants need to be assessed [2]?

In our Unit, based on scientific literature data, we encourage fresh milk breastfeeding in preterm newborns. In the case of VLBW preterm neonates (gestational age <30 weeks, or with a birth weight <1000 g), we evaluate the mother's serological condition in relation to HCMV. Maternal milk from seropositive mothers is frozen at -20°C for 96 hours before feeding offspring. This procedure is followed for 2 months, coinciding with the maximum peak of virolactia. If mothers are seronegative, raw breastfeeding is encouraged.

Declaration of Interest: The authors declare no conflicts of interest.