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TRANSMISSION OF CYTOMEGALOVIRUS VIA BREAST MILK IN LOW BIRTH WEIGHT AND PREMATURE INFANTS: A SYSTEMATIC REVIEW

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Abstract

The human cytomegalovirus, also known as HCMV, is a herpesvirus that infects around sixty percent of people living in industrialized nations and more than ninety percent of adults living in developing nations. Because infections are typically kept under control by a robust immune response, patients typically have either no symptoms at all or only mild symptoms. Breast milk is regarded as the best diet for newborns because of the anti-infectious properties it possesses in addition to its high nutritional value; yet, breast milk can also act as a vehicle for the transmission of infectious diseases such as viruses and bacteria. Breast milk is the vehicle via which the great majority of human cytomegalovirus (HCMV)-seropositive women pass the virus on to their children. Because their mothers have antibodies that are specific to HCMV, full-term neonates who acquire infections during pregnancy normally show no symptoms and do not experience any difficulties. In contrast, preterm neonates with very low birth weight (VLBW) are more likely to develop symptomatic infections, such as neutropenia, thrombocytopenia, sepsis-like syndrome, and, less frequently, pneumonia and enteric infection. These infections are more likely to occur in VLBW premature newborns. It would suggest that infections that are acquired postnatally clear up on their own without influencing the clinical result. We observe that there is still a risk of ASI-acquired CMV infection in premature newborns whose mothers have a positive CMV antibody test, although the rate of CMV infection is higher in premature infants who are fed fresh breast milk.

Keyword: *Breast milk; Cytomegalovirus; Low birth weight; Premature; Transmission*

INTRODUCTION

Human cytomegalovirus (HCMV) is a herpesvirus that infects 60 percent of adults in industrialized countries and more than 90 percent of adults in underdeveloped countries. It is usually controlled by a strong immune response, thus infections are asymptomatic or have minor symptoms. However, if the immune system is weakened, HCMV can replicate at a rapid rate and produce significant end-organ disease. There has been significant progress in understanding the natural history and pathogenesis of HCMV infection and illness in the immunocompromised host.[1–3]

Nearly 96% of seropositive mothers have CMV reactivation, which is defined as the presence of viable virus or CMV deoxyribonucleic acid (DNA) in breast milk. The transmission rate of CMV from CMV-positive breast milk to premature neonates ranges from 37 to 87%, according to previous studies.[4] Moreover, preterm infants were more susceptible to CMV infection than term infants. In addition, preterm neonates exhibited poor outcomes such as abnormal laboratory findings, a sepsis-like syndrome, and even neurologic sequelae.[5,6]

Due to its nutritional value and anti-infective components, breast milk is considered the optimal food for infants, but it can also serve as a vector for viral and bacterial infection. The vast majority of human cytomegalovirus (HCMV)-seropositive mothers transmit the virus to their infants via breast milk. Perinatally acquired infections in full-term neonates are typically asymptomatic and without complications due to maternal HCMV-specific antibodies.[7]

In contrast, very low birth weight (VLBW) preterm neonates are susceptible to symptomatic infections, including neutropenia, thrombocytopenia, sepsis-like syndrome, and, less frequently, pneumonia and enteric infection. Postnatally acquired infections appear to resolve spontaneously without affecting the clinical outcome.[8] The majority of cCMV newborns have no clinical indications at birth, but 10-15% will suffer hearing loss. CMV prevention measures are restricted, and antiviral medication with valganciclovir for 6 months is the standard of care for babies with symptomatic cCMV.[9,10]

The goal of this study is to learn more about the transmission of CMV through breast milk in low birth weight and premature infants.

METHODS

The author ensured that the study was carried out correctly by complying to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 standards. These guidelines ensured that the research was carried out correctly. This is done to ensure that the conclusions of this study are correct. By examining or analyzing past research on the subject, this literature review seeks to explain the transmission of CMV via breast milk in low birth weight and premature newborns. The main point of this study is to underline how crucial the topics raised are to examine.
The researchers who took part in the study had to have the following qualifications: 1) The manuscript must be written in English and the primary emphasis of the study must be the transmission of CMV via breast milk in low birth weight and premature children in order to be accepted for publication. 2) This assessment considers publications published after 2013 but before the time period covered by this systematic analysis. Editorials, submissions without a DOI, already published review articles, and entries that are substantially identical to previously published journal publications are examples of research that is not permitted.

We used "transmission"; cytomegalovirus"; "breast milk"; low birth weight" and "premature infants" as keywords.The search for studies to be included in the systematic review was carried out from May, 20th 2023 using the PubMed and SagePub databases by inputting the words: *("transmissability"[All Fields] OR "transmissable"[All Fields] OR "transmissibilities"[All Fields] OR "transmissibility"[All Fields] OR "transmissible"[All Fields] OR "transmissibles"[All Fields] OR "transmission"[MeSH Subheading] OR "transmission"[All Fields] OR "transmissions"[All Fields]) AND ("cytomegalovirus"[MeSH Terms] OR "cytomegalovirus"[All Fields] OR "cytomegaloviruses"[All Fields]) AND ("milk, human"[MeSH Terms] OR ("milk"[All Fields] AND "human"[All Fields]) OR "human milk"[All Fields] OR ("breast"[All Fields] AND "milk"[All Fields]) OR "breast milk"[All Fields]) AND ("infant, low birth weight"[MeSH Terms] OR ("infant"[All Fields] AND "low"[All Fields] AND "birth"[All Fields] AND "weight"[All Fields]) OR "low birth weight infant"[All Fields] OR ("low"[All Fields] AND "birth"[All Fields] AND "weight"[All Fields]) OR "low birth weight"[All Fields]) AND ("infant, premature"[MeSH Terms] OR ("infant"[All Fields] AND "premature"[All Fields]) OR "premature infant"[All Fields] OR ("premature"[All Fields] AND "infants"[All Fields]) OR "premature infants"[All Fields])* used in searching the literature.

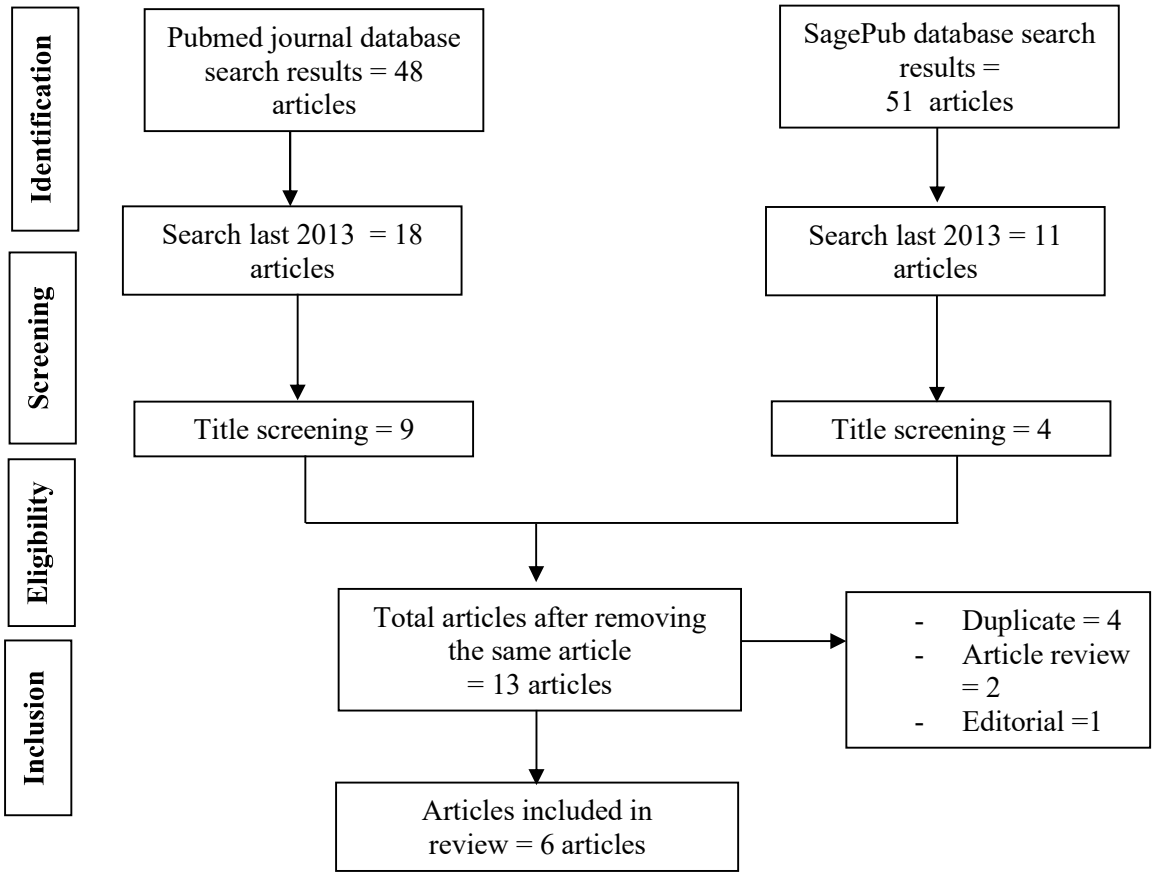

Figure 1. Article search flowchart

The writers determined the eligibility of each study based on its abstract and title. The writers then chose past studies for this paper. This finding was obtained after reviewing a large number of studies that followed the same trend. English contributions must be previously unpublished. Only studies that met all of the criteria were included in the systematic review. The search only yields relevant results. Unsatisfactory research is ignored. The study will then be scrutinized. Names, authors, publication dates, locations, study activities, and parameters were discovered in this investigation.

Before picking which publications to investigate further, each contributor conducted their own research on the research provided in the publication's title and abstract. Then, we'll look at all papers that fulfill the review's inclusion criteria and are thus excellent enough to be included. Then, based on our findings, we'll choose which publications to include in the review. This criterion is used to select manuscripts for evaluation. To make selecting articles to review as simple as feasible.

RESULT

In vitro study by Weimer (2021)[11] showed 90% inhibitory concentration (IC90) of purified human lactoferrin against CMV was 2.08 ng/mL. The IC90 values for bovine lactoferrins were > 10-fold higher. All breast milk (median: 3.3 106 ng/mL) and saliva (median: 84.4 ng/swab) samples contained lactoferrin. The average amount of CMV in breast milk was 893 copies/mL. There was no correlation between lactoferrin concentration in breast milk and CMV burden. Five infants acquired postnatal CMV. There was no difference in the concentration of lactoferrin in saliva or breast milk between mother–infant pairs with and without postnatal CMV infection.

Ricardo, et al (2013)[12] showed 1.48% of the newborns was found to be present congenital CMV infection. In four out of the 36 (11.1%) newborns who were examined, post-natal infection was found to be present. CMV excretion was found in 43 of the 116 moms who were tested. Gestational age at birth was lower in newborns whose mothers had excreted CMV than it was in children whose mothers had negative findings (p = 0.07; 33.1 weeks against 34.2 weeks; respectively).

Josephson, et al (2014)[13] conduted a study with CMV seroprevalence was 76.2% (n = 352) among the 462 enrolled mothers. In 539 VLBW infants, the cumulative incidence of postnatal CMV infection at 12 weeks was 6.9% (95% CI: 4.2%-9.2%); among the 29 infants with postnatal CMV infection, 17.2% developed symptomatic disease or died. 57.5% (n = 311) of the infants received a total of 2061 transfusions; none of the CMV infections were associated with transfusion, resulting in a CMV infection incidence of 0.0% (95% CI, 0.0%-0.3%) per unit of CMV-seronegative and leukoreduced blood. 27 of 28 postnatal infections occurred in neonates fed CMV-positive breast milk (incidence at 12 weeks: 15.3%; 95% confidence interval [CI]: 9.3%-20.2%).

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Weimer, 2021[11]	United State of America (USA)	In vitro study	No describe	In a laboratory setting, lactoferrin is able to inhibit CMV replication; however, the amounts of this protein found in human breast milk and saliva are probably too low to allow for efficient CMV inhibition in vivo.
Ricardo, 2013[12]	Mexico	Cross sectional study	135 infant	There is a high incidence of CMV excretion in breast milk, which is linked to both congenital and postnatal infection. In order to evaluate the impact of CMV infection during pregnancy and its effects on newborn outcomes, additional research is required.
Josephson, 2014[13]	USA	Prospective cohort study	539 VLBW infants	The transmission of CMV to very low birth weight newborns can be effectively prevented through the transfusion of blood products that are CMV-seronegative and leukoreduced. Breast milk provided by the mother is the most common route of transmission of postnatal CMV infection to newborns whose care is administered via this transfusion-based strategy.
Omarsdottir, 2015[14]	Sweden	Randomized controlled trial	140 extremely preterm (EPT) infant	The routine freezing of all maternal milk (MM) did not have an effect on the rate of CMV transmission; nevertheless, there is a possibility that it helped to prevent fungal sepsis in EPT infants. This observation calls for additional research to be done.
Maria, 2015[15]	Spain	Prospective cohort study	160 infant	The rtPCR method is useful for detecting moms who have high viral loads of CMV-DNA in their milk. It can also be of assistance in determining whether or not to freeze the breast milk of premature children who are younger than 28 weeks old.
Hosseini, 2016[16]	Iran	Randomized controlled trial	169 infant	According to the results of the study, using the freeze-thaw procedure is an efficient way to reduce the amount of CMV that is present in breast milk samples.

Other study showed congenital CMV infection was identified in 2% of infants screened. The CMV transmission rate in neonates fed with CMV-DNA positive breast milk was 8% in the intervention group (3 of 37) and 6% in the control group (2 of 33). All CMV-infected infants were asymptomatic. In the final per-protocol analysis, 56 infants from the intervention group and 65 infants from the control group participated. Both groups had comparable rates of neonatal mortality (7% vs. 6%). Except for late-onset Candida sepsis, which was more prevalent in the controls (12% vs. 0%), neonatal morbidity was comparable.[14]

Maria, et al (2015)[15] conducted a study with 160 infant. They showed PCR analysis of breast milk samples from 92 mothers (92 of 131, or 70.2%) revealed the presence of CMV. PCR detected CMV infection in thirteen children, and four of them (30.7%) displayed clinical symptoms. There were no statistically significant differences in morbidity between symptomatic and asymptomatic patients; however, the average length of hospitalization for symptomatic children was longer than for asymptomatic children ($P < 0.05$).

Other study in Iran showed virus DNA in four of twenty-five (16%) breast milk samples after freezing and thawing, but no CMV DNA particles in twenty-one (84%) of them. Before freezing, the mean viral burden in these samples was 76.04 ± 34.08 copies/L (20-135.00 copies/L), while after freezing it decreased to 6.75 ± 4.34 copies/L (0.00-13.00 copies/L). The viral burden of the samples decreased significantly after freezing ($p = 0.001$).[16]

DISCUSSION

Cytomegalovirus, sometimes known as CMV, is a common virus that can cause anything from no symptoms at all to severe end-organ dysfunction in immunocompromised people who have congenital CMV illness. Herpesviruses, also known as Herpesviridae or human herpesvirus-5 (HHV-5), are the family of viruses that include human cytomegalovirus as a member. Infections caused by the human cytomegalovirus are typically associated with the salivary glands. In healthy individuals, a CMV infection may not manifest any symptoms; nevertheless, in immunocompromised patients, the virus may pose a serious risk to life. The role that health professionals playing together plays in the management of cytomegalovirus is discussed in this activity.[17]

Unlike cCMV, which is thought to be passed to the fetus via maternal viremia, pCMV from breast-feeding is likely transmitted transmucosally. CMV transmission anatomy is unknown. Most VLBW newborns are not ready for full oral

feedings, hence gastric or jejunal enteral nutrition is used. This suggests that small bowel mucosa-transmitted breast-milk-associated pCMV infections may be common. Studies show that CMV infects polarized Caco-2 intestinal epithelial cells at the basolateral surface. Alternatively, pCMV infection may start in the oropharyngeal or nasopharyngeal epithelium and spread to regional lymph nodes, the reticuloendothelial system, and many end organs.[7,17]

This transmucosal route may be the most common in term babies. Although epithelial cells are thought to be the location of initial replication, CMV may infiltrate susceptible hosts via trans-olfactory infection. Both experimental virus absorption and littermate transmission of the murine CMV use a nasal / transolfactory mode of infection.[18] After trans-olfactory spread, salivary glands sustain transmissible infection. Other studies of MCMV infection in neonatal mice have shown that intraperitoneal injection of MCMV-positive breast milk is sufficient to commence infection, demonstrating that transmission via a mucosal surface is not necessary for milk to be infectious.[19]

CMV is reactivated during breastfeeding in up to 70%–95% of CMV-seropositive mothers; CMV shedding into breast milk is reported in 67%–92% of CMV-positive mothers and in 40%–70% of all women. CMV is reactivated during lactation in up to 70%–95% of CMV-seropositive mothers. CMV reactivation in the postpartum period may be caused by the suppression of cellular immunity; however, low levels of CMV DNA may not be observed soon after birth due to the presence of CMV-neutralizing or -inhibiting IgA antibody, tumor necrosis factor-, interferon-, and lactoferrin in colostrum. This could explain why low levels of CMV DNA are not observed soon after birth.[12,14,16,18,20]

It is surprising that not all newborns exposed to CMV-positive breast milk become sick. CMV reactivation in breast milk occurs in ~90% of seropositive breastfeeding women, according to research. In the neonatal intensive care unit (NICU), only 20% of newborns fed CMV-positive breast milk become sick. Infection-prone infants have been studied for adaptive immunity deficiencies. One study examined how milk CMV load and symptomatic pCMV transmission related to CMV-specific cellular and humoral immune responses in 30 seropositive mothers of VLWB preterm infants.[12,20]

After ruling out other potential origins of CMV infection, such as congenital infection, infection during birth, or horizontal infection after delivery including transfusion, the researchers were able to confirm that the infection was transmitted through breast milk. In all but one of the studies, a congenital CMV infection (defined as a positive result within three weeks of birth) or an infection during delivery (defined as a positive result in the analysis of swabs taken from the baby's body surface) was ruled out. Congenital CMV infection was defined as a positive result within three weeks of birth.[18]

Diosi et al. were the first to show that CMV could be found in human milk and that CMV cases in newborns were linked to the virus getting into breast milk. Breastfeeding made the chance of getting CMV 1.6 times more likely than formula feeding.30 Rates of CMV infection in breastfed babies were reported to be anywhere from 5.7% to 60%. By gestational age, the risk of CMV infection was higher in babies born after 23–24 weeks, 17.1% in those born after 25–26 weeks, 15.2% in those born after 27–28 weeks, and 7.1% in those born after 29–30 weeks.[21]

Enteral feeding procedures for infants born to CMV-seropositive mothers after fewer than 32 weeks of gestation or with birth weights of 1,500 grams or less differ from region to region. These protocols are intended for infants born at less than 32 weeks of gestation or with birth weights of less than 1,500 grams. The results of a questionnaire regarding enteral feeding methods in neonatal intensive care units (NICUs) in Switzerland, Germany, and Austria suggested that breast milk was given after either short-term or long-term pasteurization, after freeze–thawing, or it was given fresh and untreated.[16,22]

CONCLUSION

We see that premature newborns with CMV-seropositive moms are still at risk of ASI-acquired CMV infection, although the CMV infection incidence is higher in premature infants receiving fresh breast milk.

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