Cytomegalovirus transmission in breast milk: integrative review

ABSTRACT
Objective: to evaluate the evidence of Cytomegalovirus transmission to the newborn through breast milk and its repercussions. Method: integrative review in order to answer the question << How the transmission Cytomegalovirus to the newborn via breast milk is being addressed in national and international scientific publications? >> For this purpose, it has been consulted LILACS databases, Web of Science, BDENF and virtual library SciELO. Results: the final sample was composed of nine articles that described preventive measures like pasteurization, cooling, freezing, and use of Ganciclovir for the neonate; the premature babies had sepsis and respiratory diseases after Cytomegalovirus contamination by breast milk, at different rates of infection. Conclusion: it became evidence disagreements in findings, especially related to epidemiological data of transmissibility by breast milk and the form of this substance offered to newborns, being indispensable to stimulate scientific production in this area in order to empower greater dissemination of this knowledge and enable new intervention strategies. Descriptors: Cytomegalovirus; Perinatal Care; Breast Milk.

RESUMO
Objetivo: avaliar as evidências da transmissão do citomegalovírus ao recém-nascido pelo leite materno e suas repercussões. Método: revisão integrativa com vistas a responder à questão << Como a transmissão do citomegalovírus ao recém-nascido através do leite materno está sendo abordada em publicações científicas nacionais e internacionais? >> Para isso, foram consultadas as bases de dados LILACS, Web of Science, BDENF e biblioteca virtual SciELO. Resultados: a amostra final foi composta por nove artigos que descreveram medidas preventivas como pasteurização, resfriamento, congelamento, e utilização de Ganciclovir pelo neonato; os bebês prematuros apresentaram sepsis e doenças respiratórias, após a contaminação por citomegalovírus pelo leite materno, em diferentes taxas de infeção. Conclusão: se evidenciaram discordâncias nos achados, especialmente relacionadas a dados epidemiológicos da transmissibilidade pelo leite materno e a forma de oferecimento dessa substância aos recém-nascidos, sendo indispensável estimular produções científicas nessa temática no intuito de potencializar maior difusão desse conhecimento e possibilitar novas estratégias de intervenção. Descriptors: Citomegalovírus; Assistência Perinatal; Leite Materno.
INTRODUCTION

Cytomegalovirus (CMV), also known as HHV-5, is a Human herpes virus belonging to the genus Cytomegalovirus and subfamily β-Herpesvirinae, OF the family Herpesviridae. The ability of latency and permanence in the host organism are peculiar characteristics of these viruses, allowing thus their reactivation in different circumstances, especially in cases of modification of the immune response such as: pregnancy, lactation, stress situations and use of immunosuppressive drugs. CMV infection can occur from the exposure of the subject to biological fluids contaminated, such as saliva, semen, vaginal secretions, urine, and breast milk, as well as by blood transfusion, organ transplantation and vertical transmission. Vertical transmission of CMV can occur for two different ways: 1) congenital infection via maternal placenta, or 2) perinatal infection during labor or postpartum. In the postpartum, breastfeeding is the main form of contamination in the newborn. Cytomegalovirus represents one of the most common etiologic agents of congenital and perinatal infection in various regions of the world, varying its incidence rate according to each socio-economic reality and historical period. In Brazil, the rate of transmission of CMV from human milk in the first eight weeks, present variable between 5% to 24%, with an average of 12%. Infection, especially in premature newborn during the first few weeks of life, can cause neurological developmental sequels, as well as hearing impairments or mental retardation. Such data highlight the importance of epidemiological studies denoting the status of perinatal Cytomegalovirus infection in Brazil, because knowing the gestational and postpartum seroprevalence of agents that can be transmitted from mother to fetus/newborn and cause disease is an essential tool for the formulation of public health policies, favoring the programmatic actions planning of prevention and assistance.

Despite the proven vertical infection rates and the possible consequences for newborns, is not advocated yet by the Ministry of Health to conduct examination for the detection of CMV in pregnant women during prenatal care, action that would be strategically effective, because it would allow the early identification of infected pregnant women. Moreover, such action would collaborate to reduce chances of infection, through the adoption of preventive measures and transmission control, thus avoiding consequent complications to the health of newborns.

Whereas it is important the development of studies on the transmission of CMV to newborn by breast milk, and pondering the scarcity of works dealing with the transmission under this approach, the present study is justified in an attempt to contribute to the expansion of knowledge of actions on maternal and child health, to postulate how objective the evaluation of the available evidence in the literature about the Cytomegalovirus transmission to the newborn by breast milk and its repercussions.

On the observations mentioned, it is considered a relevant study by encouraging the identification of interventions that provide improvements in maternal and child health, as well as reducing the risk of contamination by the virus. It is important because it demonstrates that the perinatal transmission of CMV should be evaluated as a theme relevant to studies at the national level, since, from the results of studies already undertaken, it is possible to offer health professionals the knowledge to qualify their performance in women’s health and the child.

METHOD

Study with a qualitative approach, carried out from the integrative review method, which follows the outline already published on literature and aims to collate, synthesize and analyze the results of primary research about the analyzed phenomenon, and, therefore, to contribute to the knowledge of the issue.

The review was carried out in five stages: problem formulation, data collection, data evaluation, analysis and interpretation of data and presenting results; and guided by the following question << How cytomegalovirus transmission to the newborn via breast milk is being addressed in national and international scientific publications? >>

The study was conducted in 2011, through online search of national and international scientific productions on Cytomegalovirus transmission through breast milk and its repercussions. The capture of these productions was processed through the Journal Portal CAPES and the Virtual Health Library (VHL), being used the databases: Latin America and Caribbean literature in Health Sciences (LILACS), Web of Science, Database in Nursing (BDENF) and the virtual library Scientific Electronic Library Online (Scielo).

The keywords used in the search were: “Cytomegalovirus, Cytomegalovirus infections”, “perinatal care” and “breast milk”, avoiding consequent complications to the health of newborns.
according to the descriptions of each by health sciences descriptors (DeCS), and employed together, the Boolean operators “AND” or “OR”, resulting in a total of 9,343 articles.

Even at this stage, it was performed a careful reading of titles and abstracts, to verify suitability the following inclusion criteria: free full-text available on electronic support during the period from 1991 to 2010, written in Portuguese, English and Spanish languages, and that makes allusion to cytomegalovirus in the abstract. Thus, 2,514 studies were pre-selected.

In order to contemplate what this study proposes, it was elected the exclusive themed publications about the transmission of Cytomegalovirus by breast milk, which is another criterion for inclusion. Articles not dealt about the object of study were discarded, presented only abstract available online and that were not in the delimited timeframe. Faced with such criteria, nine articles were selected, of which two were in LILACS, two in Scielo and five in Web of Science, not being selected articles on BDENF.

Then, the data collection proceeded from the careful review of titles, abstracts and contents of articles. To this end, it was devised a methodological instrument which included the following aspects: article identification data (title, authors, journal, year of publication, key words), objective/research question of the studies, methodological delineation, results, limitations and recommendations.

The instrument allowed the cataloging articles and registration of the information contemplated in its aspects. This step was important because it allowed researchers to the insightful evaluation of the data collected, separating those which, in fact, have importance for the study.

Data analysis was guided from the outline of analysis and interpretation of information described in the literature, which consists in the synthesis and comparison of data recorded in the data collection instruments and discussion of the extracted data of articles, as well as the comparison between the results of the studies analyzed, delimiting priorities for future research. To carry out presentation of findings it was prepared a figure that adds the organization and structure of data content and demonstrates the information obtained.

As for the ethical aspects, it should be noted that the principles of authorship and referencing of articles analyzed were respected, thereby ensuring the authenticity of ideas, concepts and results to the authors surveyed. As the study, it configures an integrative review of existing literature and available on the subject. It didn’t require their submission to a Research Ethics Committee. However, the project was submitted to the Research Committee of the Nursing School of the Federal University of Rio Grande do Sul (COMPESQ/EENF-UFRGS) due to registry.

RESULTS AND DISCUSSION

Nine articles were analyzed that met the inclusion criteria established in advance. Among them, only one was written in the Portuguese language, being the earliest published in 1991. The others were published in the English language, demonstrating the international predominance in research that relate to the subject under study.

In view of a better description of the results, the data are organized and presented in Figure 1, considering the variables: authors, year of publication, methodological delineation, the study objectives and main results and considerations.
Oliveira GC de, Gonçalves AC, Ferreira GE et al. Cytomegalovirus transmission in breast...

Figure 1. Presentation of selected articles according to authors, year of publication, delineation, objectives of the study and principal results and considerations, 2011.

It is observed in Figure 1, as for articles published in the period from 1991 to 2010, that an article was published in 1991, one in 2001, an article in 2002, one in 2003, three articles in 2005, an article in 2006 and one in 2010. Although there are a greater number of publications from 2005, the equivalent of 56% of the articles found is in the literature that...
studies on the transmission of CMV through breast milk has been held since 1970.\(^7\)

The origin of the researches which address the subject is predominantly North American (67%), however, the database search showed two Japanese studies (22%) and a Brazilian study (11%). With respect to the methodological delineation of articles, three articles are bibliographic reviews, four are prospective cohort studies, a systematic review and a magazine editorial.

The publications included in the study were prepared mainly by health professionals in the area of medicine, specifically Pediatrics, with contributions from nutritionists in some research. Nurses are not part of the authorship of the studies analyzed. These data underline the necessity of nursing to enter in search terms with this issue, since it is a rather professional category present in attention to women's health, neonatal and pediatric.

After selecting all the material found by relevance on the subject, the results have been grouped in the following pillars: Cytomegalovirus transmission from breast milk and repercussions of Cytomegalovirus infection through breast milk and preventive measures.

- Transmission of cytomegalovirus in breast milk

The presence of CMV in breast milk was suggested for the first time in the early 70, when were found that infected babies not congenitally were diagnosed with potential risks for viral infection at the end of the first month of life. Historically, the acquisition was attributed to perinatal transmission through cervix secretions. However, the absence of CMV in the maternal cervix by smears in many cases suggested another source of transmission.\(^7\)

Studies conducted in the early 1990 pointed to the occurrence of congenital infection in 0.2% to 2.2% of newborns, with higher incidence in populations of low socioeconomic class. In perinatal infection, as a result of viral transmission during childbirth by maternal milk, for blood transfusions or secretions, performed more often than the congenital, with incidences ranging from 5% to 38%.\(^6\) More recently in Israel was identified a 5.7% infection rate among newborns fed with breast milk of infected mothers.\(^11\)

Most of the human herpes virus family viruses are transmitted by cell-cell contact, as in the case of Cytomegalovirus transmission from breast milk. Infants are susceptible to CMV infection through breastfeeding. Premature infants with low concentration of serum antibodies can acquire CMV from the fresh breast milk containing the virus. However, the clinical significance of Cytomegalovirus infection in infants by breastfeeding is not completely clarified. Studies show that the seropositive for antibodies against CMV is indicative of latent infection, i.e. there is presence of viral genome into the host.\(^12,13\)

CMV transmission from mother to baby is more likely to occur when the viral load in breast milk is greatest, being the high rate of seropositive of mothers, probably, the main indicator of acquiring the virus. Therefore, both the genome of CMV, as infectious viruses were detected significantly earlier in the milk of mothers previously infected by the virus, being most frequently observed than in other sources of neonatal infection, such as vaginal secretions, urine and saliva. The infestation appeared to be more closely associated with vertical infection than to contact with the genital tract, being that children fed with breast milk for more than a month were infected more frequently.\(^6,7,10,11\)

Besides the way it is transmitted CMV to newborn through breastfeeding, studies show that the risk of acquisition of Cytomegalovirus is 5% to 38%, although this index is considered high. These studies also point out the relationship with the high prevalence of this virus in the population, since seropositive mothers are the main sources of transmission.\(^7,10\) However, in subsequent research was established even greater transmission (about 70%) in relation to the consumption of contaminated breast milk.\(^12\)

In counterpoint, some researchers showed that cool defrosting breast milk, used for feeding babies, would have a transmission rate of 5.7% in the first eight weeks of life,\(^11\) although it has already been seen in the transmission of CMV in only 10% of premature infants, even considering the high detection rate and DNA amount of CMV in breast milk (87.5%).\(^6\) Later, it was appointed in systematic review the transmission of Cytomegalovirus via human milk range from 5.7% to 58.6% of positivity in children.\(^13\)

It was found remarkable differences in the studies reviewed, as regards the percentage of detection of CMV in breast milk, and they may be associated with methodological delineations of the studies, being related to characteristics of the population/sample (distinct gestational age and birth weight), or the different methods of analysis proposed by each research.
Similar finding had already been mentioned in one of the articles, revealing that the difference in the results of research could be associated to the study population, the storage of breast milk samples and clinical analysis of standard samples. In the same perspective, another study\textsuperscript{14} points the need for more detailed surveys to better characterize the transmission of CMV to neonate by breast milk, as well as the relationship between breastfeeding and symptomatic infections.\textsuperscript{6}

Regardless of the differences in the results, the importance of breastfeeding the newborn in those articles was considered. The beneficial effects of human milk were identified in research with premature babies fed with contaminated milk.\textsuperscript{15} Although the rate of acquiring of the virus referenced was almost 25\%, only some of the children were symptomatic after infection. The study demonstrated that occasionally were observed these children a light clinic decompensation, called septic syndrome, which rarely need respiratory support. However, despite the viral acquisition, there seems to be a greater number of episodes of clinical deterioration in such children.\textsuperscript{15}

Despite the human milk to premature infants and other high-risk babies through breast feeding be recommended, decisions on breastfeeding by seropositive mothers for CMV should be made with caution, being necessary to weigh the potential benefits of human milk versus the risk of transmission of CMV.\textsuperscript{13} This is because premature newborn have immature immune system and, consequently, higher risk of acquiring CMV infection through breastfeeding. Thus, breastfeeding should be cautious, which makes essential the investigation of viral agents in human milk, in order to avoid possible damages to premature babies.\textsuperscript{7,13}

In contrast, other scholars contend that the policy should be to encourage breastfeeding of babies of low weight with their own cool breast milk.\textsuperscript{11} Furthermore, the World Health Organization and the United Nations Children's Fund (UNICEF) have joined efforts in the establishment of a policy of encouraging breastfeeding.\textsuperscript{16} Though, as very low weight premature neonates receiving human milk from mothers with seropositive are those that have higher risk of developing CMV infection, a high level of tracing is required, including reference neonatal screening for Cytomegalovirus.\textsuperscript{11} Such organs still point out that, although not completely effective, a feeding of premature babies by frozen human milk may be considered beneficial.\textsuperscript{11}

From the discussion of the data obtained in this integrative review, it might be noted that the authors have similar information on some points, such as the greater likelihood of premature newborns acquire CMV infection and the repercussions of the pre-term newborn Cytomegalovirus. However, they argued in others, especially in relation to rates of transmission of CMV to newborns and to providing breast milk to premature newborn, demonstrating the need for further research to elucidate as transmission of CMV from the mother to the newborn through the milk and to establish more accurately the magnitude of the consequences of perinatal infection. In this way, it will be possible to establish a consensus and, with it, a possibility of standardization of behaviors related to providing breast milk to infants at greatest risk for neonatal morbidity and mortality.

\textbf{Effects of Cytomegalovirus infection through breast milk and preventive measures}

Scientific productions analyzed have repercussions of Cytomegalovirus infection in the newborn, which characterize the population affected by this loss of health and indicate that premature newborns are most susceptible to the disease. Among the studies found, six articles discussed the repercussions to the newborn and showed the possible health problems to this population group.

In two of the productions, it was evidenced that the increase in the practice of breastfeeding has a big effect on the epidemiology of Cytomegalovirus infections. The researches were found in prospective studies that showed high incidence of CMV infection in premature infants of sero positive mothers, for they present a higher risk of acquiring CMV early and have symptomatic infection.\textsuperscript{12,14} One of these studies estimated that children who are not breast-fed have a six times higher risk of death from infectious diseases in the first two months of life, however, claim that the term newborn can be breastfed when the mother has the virus in his milk, since such babies have better functional ability of the immune system.\textsuperscript{12}

The research value therapeutic and preventive measures are essential for the combat of cytomegalovirus in children. The contraindication of breastfeeding is an important theme of reflection in relation to preventive measures of Cytomegalovirus transmission to the newborn. Mothers would face difficulties they cannot breastfeed, because such an act represents a form of mother/baby interaction.\textsuperscript{7,17} Even considered
as a factor which causes contamination of the child, breastfeeding is recommended because it has arguably nutritional importance. Deprive the neonate of human milk may increase morbidity and mortality due to complications such as sepsis and Necrotizing Enterocolitis.5

It is important to note that the puerperium is an often confrontational period, and when there is presence of Cytomegalovirus merged with the possibility of worsening of the health of the child, this time the woman is even tenser. The reflection on the puerperium with Cytomegalovirus, the study of the best nursing actions and the pursuit of quality of life of who has recently given birth and the baby are challenges found in practice that can assist in reducing the numbers of perinatal transmission.

In contrast to the full-term babies, premature infants have an immature immune system and are born before the transfer of the majority of protective immunoglobulins, which occurs after 28 weeks. This can make them more susceptible to CMV infection through breast milk. Scholars have shown that 15% to 17% of premature babies later acquired sepsis and respiratory diseases.7

Researchers showed in breast milk the most important source of CMV infection during the first year of life, stating that, since 1983, signs of neutropenia, thrombocytopenia, Lymphocytosis and symptoms of hepatosplenomegaly were already associated with cytomegalovirus in children infected through breast milk.13 In that context, some of the research shows that 12% of premature neonates investigated developed septicemia.14 In 1998, high rates of very low birth weight newborns infected were reported on the basis of possessing greater risk of symptomatic infection. However, through the analysis of studies, the average rate of symptomatic disease was 3.7% in children, with rate of 0.7% for severe sepsis and infection rates and disease vary widely from study to study.13

Perinatal CMV infection in premature or low birth weight children from breast milk may result in severe acute illness. Symptoms include acute deterioration, such as sepsis, and in some children, apnea and bradycardia, as well as leukopenia and thrombocytopenia.18 Preventive methods varied in order to eliminate the virus in milk have been studied, including freezing, pasteurizing and quick heating. Pasteurization is highly effective in removing the viral CMV, but will also damage lymphocytes and immunoglobulins of breast milk. In contrast, refrigeration and freezing of milk are less harmful to the protection components in milk, but are much less effective in removal of CMV,7,13 since the virus can still be detected using techniques sensitive to culture after 10 days of freezing in a domestic freezer, demonstrating the viability of the virus after the freezing process.7 But, in one of the articles was presented that freezing breast milk to -20° C for seven days can inactivate the virus without affecting the immune and nutritional qualities of breast milk and therefore can be a protection for the premature baby until the serum antibody against CMV received by increasing breastfeeding.12

Anyway, the eradication of CMV in human breast milk, without diminishing its quality or immune nutritional benefits, would be a first step to protect premature neonates of CMV infection through breast milk. Holder pasteurization of milk effectively eliminates viable CMV, but obviously that immunological components decrease in breast milk. Cold treatment or freezing breast milk to -20° C doesn't seem to decrease the immunological components in human milk or adversely affect its nutrients. However, there are still concerns about what could happen with high viral load and which the freezing period is necessary in order to achieve 100% inactivation.18

A suggested approach in one of the selected articles was to use milk donated by seronegative mothers for Cytomegalovirus. However, there are concerns about other potential infections, but the milk is usually unique to each newborn and, therefore, it is possible not to meet the specific needs of premature babies. In addition, most innovative methods for removal or inactivation of CMV in breast milk are needed, since there is no evidence for the use of antiviral in mothers and their babies as a preventive measure.7

In antithesis to such propositions, subsequent research has shown that Ganciclovir has been used in individual cases of symptomatic congenital Cytomegalovirus or postnatal acquired elementary in premature babies. According to the study, Ganciclovir produces a reduction in viremia during therapy, but there is a rebound effect after discontinuing the medication. The remedy seems to prevent deterioration of hearing function in six months of treatment in children infected with the disease symptoms, however, causes significant damage to the health of newborns, such as neutropenia in more than two-thirds of the babies after six weeks of treatment.18

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Anyway, clinically practical methods for the inactivation of CMV in breast milk, without diminishing their immunological action and the benefits of nutrients require additional review, and its effectiveness in preventing transmission of CMV needs to be tested in prospective clinical trials. The additional assessment of therapeutic benefit and risks of antiviral therapy should have continuity.

In summary, from the analysis of these results, there is greater similarity between the studies about the information regarding the repercussions of cytomegalovirus in newborns and among the possible preventive measures, but there is still a need for research that will contribute to a greater understanding of the subject, providing ducts and universal guidelines for maternal and child health in relation to the transmission of cytomegalovirus in the newborn by breast milk.

**CONCLUSION**

By this integrative review, it was sought to learn how the transmission of cytomegalovirus in breast milk, and its repercussions have been addressed in scientific publications in the area of health and nursing care.

The synthesis of articles has shown discrepancy between various research results that address the theme, being notable disagreements in findings, especially related to epidemiological data of transmissibility by breast milk and the shape of the product offering to newborns, specifically at pré-terms babies. This fact reveals a troubling issue for public health and which justifies the continuation of more comprehensive studies with this objective, both at national and international level.

It was evidenced the scarcity of studies in the databases searched, including one Brazilian study among the nine articles found, requiring the development of new research in the country, once epidemiological data of the Brazilian in the newborn Cytomegalovirus would be fundamental for defining the risk of the disease, with a view to programming of health actions directed to the subject in question. Given this, the construction of a closer look to the subject well investigated constitutes a challenge, especially in the field of nursing, considering that the salvaged publications were predominantly carried out by medical professionals the pediatric area. It is worrying not to conduct studies on the subject in the field of nursing, if considered that this group of professionals, especially nurses, has key role in maternal and child care.

Among the limitations identified from the development of this study, it should be noted the fact that the investigated productions, mostly, were implemented in other contexts, from populations with different profiles found on the Brazilian reality, especially with regard to socio-economic aspects. Thus, it is suggested that the results obtained from these studies should be used with caution in our midst for the definition of conduct clinics or, even, in relation to decisions about breastfeeding.

It is expected, with this research, to contribute to the professionals and health managers to reflect on the importance of knowing in more depth the Cytomegalovirus transmission to the newborn and its repercussions, aiming at implementing health actions more effective, based on scientific evidence, capable of favorably reflected in the health indicators, especially newborns, due to their fragility and susceptibility to diseases that can compromise their survival or quality of life.

It is believed that conducting research aimed at understanding the Cytomegalovirus transmission to the newborn by breast milk, and to assess its impact, could be an initial strategy in the process of creating preventive and curative actions proposed to investigate the need and viability of the inclusion of interventionist measures in prenatal women, as well as the transformation of the teaching-learning process in this theme, enabling new ways to watch mother and child population.

**REFERENCES**


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