Research Summary

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Transmission of Cytomegalovirus Via Breast Milk to the Prematurely Born Infant: A Systematic Review.


Background:
The purpose of this systematic review was to analyze data related to breastmilk-acquired CMV infection in preterm infants, including long-term sequelae of infection.

The authors analyzed 26 prospective studies published between January 1966 and December 2008 of CMV transmission in preterm and/or low birth weight infants. Studies analyzed varied in design, infant inclusion criteria, and laboratory evidence of CMV infection. In some studies, breastmilk was pasteurized or frozen prior to feedings, in others it was given fresh. Four studies were case reports and five studies focused long-term outcomes. The remaining studies were clinical research of CMV transmission in hospitalized preterm infants.

Results:
• In CMV-seropositive mothers who were expressing milk for their preterm infants:
  • A median of 87% had CMV detected in their breast milk.
  • A median of 20% of their infants acquired CMV. The range of infection was 5.7-58.6%.
  • A median of 3.7% of their infants had laboratory and/or clinical indices of infection (mean 9.3%, range 0-34.5%). The most common signs and symptoms were neutropenia, thrombocytopenia, hepatitis, elevated liver enzymes and hepatosplenomegaly.
  • Sepsis-like symptoms due to CMV infection occurred in a median of 0.7% of these preterm infants (mean 3.5, range 0-13.8%). Sepsis-like symptoms were not specifically identified.
  • The risks of neurosensory or developmental delays were generally low and not significant.

Conclusions
• The risk of CMV acquisition and clinical symptomatology is low.
• When mothers are CMV-seropositive and infants are less than 32 weeks, the authors recommended an individualized clinical approach to breastmilk feedings rather than a generalized approach such as routine pasteurization or freezing.

Addendum

Kurath and Resch published a follow-up letter to the editor in *Pediatric Infectious Disease Journal* in which they proposed a clinical algorithm in cases of CMV-seropositive mothers who wish to provide breastmilk to their preterm infants. The algorithm starts with a stable preterm infant. If parental consent is obtained, fresh breastmilk is given and the infant is tested weekly for CMV. If an infected infant exhibits signs and symptoms of CMV infection, fresh breastmilk feedings are withheld until the infant is greater than 32 weeks.

**Commentary**

In this systematic review, Kurath *et al.* examined the short and long-term outcomes of preterm infants who become infected with CMV via maternal breastmilk. As with most meta-analyses or systematic reviews, studies evaluated varied in methodology, testing procedures, populations and outcomes. The purpose of this review was to combine multiple studies to get a broader perspective on the problem of breastmilk-acquired CMV in preterm infants. As is common in this type of research, statistical results are reported as ranges of occurrence but also as medians and means. When wide variations in ranges occur, median values are usually more accurate indicators of the data as they buffer the effects of outliers or extremes.

This analysis of multiple studies suggests the majority of women of childbearing age are CMV-positive and more than three-quarters of CMV-seropositive women shed the virus in their breastmilk. Of preterm infants receiving breastmilk from CMV-positive mothers, CMV infection occurs at a rate of approximately 20%. A small percent (median rate of 3.7% or mean of 9.3%) of preterm infants of breastfeeding seropositive mothers will develop symptomatic CMV infection. Symptoms vary widely in terms of severity and can include one or more of the following: hepatitis, pneumonia or pneumonitis, neutropenia, thrombocytopenia, elevated liver enzymes, hepatosplenomegaly, gray pallor, fever and hyperbilirubinemia.¹⁻⁴ The most commonly reported single symptom is neutropenia alone without other indications of illness.⁵⁻⁶ In studies reporting symptomatic infections in preterm infants, the infants generally recover spontaneously without evidence of long-term consequences.¹⁻⁵,⁷⁻⁸,⁹

Of greatest concern to researchers, health care providers and parents is a severe CMV sepsis-like syndrome evidenced by a very small percent of preterm infants. This analysis by Kurath and colleagues suggests a median of less than 1% of preterm infants of CMV-positive mothers will demonstrate symptoms of severe infection. (Of note, Kurath *et al.* do not report any deaths in infants with breastmilk-acquired CMV.) In a separate review of multiple clinical and case studies, Hamprecht *et al.*² reported very similar results and infant outcomes. Their total sample size was more than 1000 infants. Unlike Kurath *et al.*, they identified two infant deaths in one study by Cheong,¹⁰ both deaths in infants with NEC and CMV.

In 1998, Vochem *et al.*¹¹ identified in five preterm infants with breastmilk-acquired CMV a pattern of more acute illness now known as sepsis-like symptoms or syndrome. These infants exhibited apnea, bradycardia, distended abdomens and gray pallor. Later studies reported similar and additional clinical findings in infected infants, many of whom were extremely low birth weight.¹⁻²,⁵,¹⁰ However, despite the severity of sepsis-like infections, almost all infants recovered and were discharged home.¹⁻⁵

After publication of their systematic review, Kurath and Resch (both physicians) published a letter to the editor¹² proposing an algorithm for individualized clinical management of CMV in preterm infants. Their
algorithm outlines a management protocol based on clinical and laboratory surveillance. If an infant becomes positive for CMV and is symptomatic, mother’s milk is stopped until 32 weeks. But some important questions go unanswered: what symptoms of CMV infection warrant intervention and what are infants missing when fresh breastmilk is withheld?


