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COMMENTARY

Cytomegalovirus in Breast Milk: Reassessment of Pasteurization and Freeze-Thawing

Commentary on the article by Hamprecht et al. *on page 529*

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Cytomegalovirus (CMV) infections are common. Primary CMV infection, which rarely causes disease in the immunocompetent individual, is followed by life-long persistence of the virus in a latent phase. In the immunocompromised patient, *e.g.* an AIDS or transplant patient, CMV is the cause of considerable morbidity and mortality. In solid organ or hematopoietic stem cell transplantation, CMV disease may occur directly through organ involvement or indirectly as an increased risk for opportunistic infections.

CMV infection may also cause serious disease in the immunologically immature fetus/infant. CMV transmitted prenatally, results in congenital infection in 0.5–2.0% of newborns in the developed world (1). Neonatal morbidity is seen in up to 10% of CMV infected newborns, and long-term sequelae (neuro-developmental handicap including sensorineural hearing impairment and mental retardation), in about 15%. Infection in any period of fetal life may cause severe handicap, although the highest risk of debilitating infection is believed to be in the early period of gestation (1,2). Postnatal infection has received less attention, although reported rates of infection during the first 6 months of life are very high up to 40% (1,2). In term infants, CMV morbidity is low with no long-term sequelae, although cases of serious disease are reported, *e.g.* in sick children with underlying disorder. CMV may be transmitted from the mother to the newborn in one of two ways: *1*) exposure to CMV in cervical secretions in the birth canal during delivery, or *2*) through virus shed in the breast milk. Protection of infants from disease has been attributed to passively transferred maternal CMV IgG as well as to other nutritional and immunological factors in the breast milk (1). However, very premature infants may be more susceptible to CMV disease since they are born before the major transfer of protective immunoglobulin (at 28 weeks), and have a very immature immune system. Significant disease, with fatal outcome, was observed in preterm infants that acquired CMV infection from transfusion of CMV seropositive blood (3–6). This problem has largely been eliminated by the use of CMV-free blood products obtained from CMV-negative donors and/or leukocyte-depleted blood.

The most frequent source of CMV infection is the secretion of CMV virus in maternal breast milk (1,2,7). Studies in the 1980s indicated a high rate of CMV compatible disease in preterm infants (8–10). In one study, 6 of 18 infants weighing less than 1500 g, and in another study 14 of 16 preterm infants developed disease by 4–6 weeks of age; of those developing disease three deaths were attributed to the CMV infection. Long-term follow-up studies of a limited number of patients suggested that early onset of CMV secretion may be a significant risk factor for severe to moderate neurologic impairment but not for sensorineural hearing loss (10–13). Prevention of CMV infection through tainted breast milk was a challenge; however, it was found that pasteurization reliably destroys virus. Unfortunately, pasteurization also destroys some of the nutritional and immunological factors needed by the preterm baby (14–15). Freezing at −20°C overnight preserved such factors and reduced infectivity by 90%; after 72 hours storage, 99%; and ≥7 days, no infectious virus was detected.

During the past decade very sensitive and rapid CMV diagnostic methods were developed and used for closer characterization of CMV secretion in breast milk and CMV transmission. In a series of studies from Germany and Japan, CMV DNA was found at some time in breast milk—predominantly milk whey—from the vast majority (88–94%) of CMV-seropositive mothers, but not in seronegative mothers (16,17). Viral shedding in breast milk is seen as early as 2–3 weeks after delivery, peaks in activity by 3–6 weeks, and usually ends in most individuals by 8–10 weeks. CMV DNA analysis (18) was more sensitive than viral culture in detecting CMV in breast milk from CMV-positive donors (1,2,9). Kinetic studies conducted on virus recovered from milk whey after concentration by high-speed centrifugation correlated with viral DNA load. In addition, detection of HCMV pp67 late mRNA was shown to be an indication of replicating virus (18). Utilizing these tests Hamprecht *et al.* approached the issue of removal of infectious CMV from breast milk without destroying nutritional-immunological factors in breast milk in a series of studies presented in this issue of *Pediatric Research* (19). Heating at

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62.5°C for 30 minutes or 72°C for 5 seconds (in thin film) destroyed viral infectivity and late viral RNA. Unfortunately, these heating methods also destroyed some of the biochemical and immunological qualities of the milk. Freezing at −20°C for 4–10 days preserved such factors, but did not effectively destroy infectivity. Preliminary studies with short time heating in thin film at temperatures below 72°C were promising.

What is the clinical impact of feeding breast milk-containing CMV to a very preterm infant?

In a 3-year prospective study of infants weighing <1500 g, exposure to CMV in breast milk yielded a high transmission rate, 38% (33 of 87 infants born at <32 weeks fed fresh breast milk containing CMV (16,20,21) showed a mean transmission time of 43 days. Half (16 of 33) of the infected infants had symptoms compatible with CMV disease: hepatopathy, neutropenia, thrombocytopenia and 4 infants had sepsis-like deterioration in the early phase of the CMV infection. All infants recovered. Early onset of CMV reactivation correlated to transmission and the status of immaturity to symptomatic disease. No negative effect on neurodevelopment or hearing was found at follow-up of 22 CMV-infected preterm infants at 2–4.5 years of age and matched controls.

Gastrointestinal signs ranging from minor and transient to severe and life-threatening and resembling necrotising enterocolitis were recently described in preterm infants with breast milk transmitted CMV infection (11 cases out of 2830 admissions to a neonatal unit (22) and a handful of case reports in the literature)—in one CMV was verified by immunohistopathology (23).

Reports from other studies demonstrate lower transmission rates and infant infections are subclinical. In a preliminary report by Mosca *et al.* (24) 5 of 20 preterm infants <34 weeks exposed to CMV positive milk were infected postnatally with no clinical signs. Intravenous immunoglobulin with high titres of CMV antibody was routinely used to prevent infections. Immunoglobulin does not prevent infection but may modify disease (25). Two other studies report CMV transmission from freeze-preserved breast milk: in one preliminary report one infant out of 18 infants (<32 weeks) had a subclinical infection (26); in another study 3 of 30 infants (<34 weeks) were infected without clinical symptoms (17).

These results indicate that there is a risk for serious disease in the very preterm child by feeding breast milk. Fortunately the rate seems low and the risk for long-term sequelae limited. Elimination of CMV from a mother's breast milk without damaging protective constituents is a goal. Pasteurization removes infectivity and should be used for donated milk. For the mother's own milk, freeze storage does not seem to be a perfect solution, but the rate of CMV transmission is likely to be lowered, and observed infections, asymptomatic. It must be noted, however, that the available studies did not include as many very preterm infants as in the German study on native breast milk nor children with underlying disease.

The diagnosis of CMV disease is difficult. Symptoms of organ involvement together with CMV detection in blood or other secretions is not enough for diagnosis of CMV disease; verification by histopathological examination is required (27). However, histopathological examination is not possible in the very preterm infant, which leaves the diagnosis of CMV disease uncertain. For this reason, continued case controlled studies of CMV in the preterm child are warranted. Moreover, additional studies are needed to address whether there are indirect effects of CMV infection as experienced in transplant patients (27) and also antiviral treatment options (28).

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