



BC Hepatitis Services

Informed Decision-making about Mother-to-Child Transmission of Hepatitis C Virus by Breastfeeding

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What information should a mother with chronic hepatitis C infection be aware of, to enable her to make an informed choice about breastfeeding her infant? The purpose of this brief overview is to summarize the most recent scientific evidence of mother-to-child (MTC) transmission of hepatitis C virus (HCV) through breastfeeding and suggest how this may be applied in clinical practice.

The Dilemma

A wide range of infant health benefits are associated with breastfeeding - nutritional, immunologic, endocrinologic, psychological, and a reduced risk of a variety of chronic diseases such as diabetes and coronary heart disease.^{1,2,3}

MTC transmission of HCV has been found to occur in about 5% of HCV-infected, HIV-negative pregnant populations, whether infants are breastfed or bottlefed.^{1,24} Scientific evidence has implicated breastfeeding in the transmission of human immunodeficiency virus type 1 (HIV-1) virus from HIV-infected mothers to their infants, lending concern that HCV may also be transmissible in an analogous fashion.^{4,5,6,7}

What factors are associated with MTC transmission of HCV?

The most important factors are detectable HCV ribonucleic acid (RNA) in maternal serum, and high maternal HCV-RNA titre.⁸ A number of co-factors in addition to breastfeeding may contribute to transmission. These include maternal and/or infant co-infection with HIV, the stage of maternal HIV infection, type of delivery (i.e. vaginal or Caesarian section), maternal injection drug use, elevated maternal serum alanine aminotransferase (ALT), infant gender, and HCV genotype.^{9,10,11,12,13}

What are limitations of the current evidence of MTC transmission of HCV by breastfeeding?

A number of studies of HCV-infected, HIV-negative mothers have reported no transmission among breastfed infants^{14,15,16,17} or no significant difference in transmission rates between breastfed and non-breastfed infants.^{18,19} However, insufficient numbers of mother-infant pairs have been studied to properly assess the role of breastfeeding.

Other methodologic limitations compromise the strength of evidence to-date. These include inadequate infant HCV diagnostic criteria (e.g. passive transfer of maternal antibody being misinterpreted as infant infection, or inadequate follow-up time), unreliable HCV-RNA assays and failure to adequately control in either the study design or analysis of other putative co-factors and their interactions.^{11,13,19,20} This latter limitation is extremely important, since it is biologically plausible for MTC HCV transmission to occur in utero, intrapartum or postpartum and some risk factors may influence transmission during all of these periods. For example in one study, half (three of six) of HCV-infected infants who had breastfed were already HCV-RNA positive on the first day of life, before any feeding had occurred.²¹

What do experts advise?

Current recommendations from various professional advisory groups such as the Canadian Pediatric Society^{22,23} U.S. Centers for Disease Control Advisory Committee on Immunization Practice and the American Academy of Pediatrics²⁴, as well as from the 1998 Canadian Public Health Consensus Conference on Hepatitis C Prevention and Control²⁵ reflect uncertainty of the risk of MTC transmission of HCV by breastfeeding. (see Appendix 1)

Can HCV-RNA be detected in breast milk?

Yes. Using reverse transcriptase-polymerase chain reaction (RT-PCR) assays, HCV-RNA has been detected in the breast milk of asymptomatic, chronic HCV-infected mothers who are not co-infected with HIV.^{15,26,27,28} HCV-RNA has been detected in both colostrum supernatant and precipitate fractions collected within 5 days^{15, 27} and one month²⁶ of giving birth. Other studies have failed to detect the presence of HCV-RNA in breastmilk.^{29,30,31} Discordance between studies may be due to differences in assay sensitivity and reliability.^{27,31}

Despite differing study findings, evidence from those studies that have detected HCV-RNA in breast milk makes HCV infection through breastfeeding biologically plausible.

Is the presence of HCV-RNA in breastmilk alone, sufficient evidence to establish that HCV is transmitted by breastfeeding?

No. It is not known whether detection of HCV-RNA in breast milk indicates the presence of intact, infectious hepatitis C virions.¹⁵ The protective role of infant host defence factors, such as the mucosal barrier of the gastrointestinal tract, or other immune factors which may alter infectivity, are incompletely understood.¹³ Infants of mothers with detectable serum HCV-RNA would likely have already encountered HCV by mucocutaneous exposure to maternal blood or body fluid during delivery.^{11,32} Lactoferrin, a protein found in breast milk has been shown to prevent HCV infection in cultured human hepatocytes,³³ although its effect in MTC-HCV transmission *in vivo* is not known.

Are HCV-RNA titres in breastmilk correlated with serum titres?

HCV-RNA titres in breast milk are significantly lower than corresponding serum titres in the same individual.^{15,26,27} HCV-RNA titres in serum have been reported to exceed

levels in breastmilk colostrum by a wide range of 10^2 to 10^7 copies/ml.^{15,27} HCV-RNA titres in breastmilk colostrum are not consistently correlated with maternal serum in studies that have examined this relationship.^{15,27,28} A postulated, biologically plausible explanation for a lack of correlation between blood and colostrum HCV-RNA titres is possible contamination of breast milk from occult hemorrhage, due to dermatitis around the breast nipples or skin abrasion from suckling.¹⁵

The quantity of breastmilk consumed by an infant, in addition to the HCV-RNA titre in breastmilk, are the main determinants of an infant's exposure to HCV-RNA from breastfeeding.

Are HCV-RNA titres in breastmilk and serum correlated with clinical symptoms and/or signs of acute hepatitis in chronic HCV-infected mothers?

One study found higher HCV-RNA titres in breast milk and serum to be associated with acute, symptomatic hepatitis in chronic HCV-infected mothers.²⁷ However, studies generally indicate a poor relationship between HCV-RNA titres and severity of liver disease in chronic HCV-infected persons.³⁴

Does postpartum MTC HCV transmission occur in mother-infant pairs in the absence of detectable HCV-RNA in maternal serum or breastmilk?

Transmission from HCV-seropositive mothers with undetectable serum HCV-RNA appears to be very uncommon regardless of mode of feeding.^{8,14,19,20} The few instances of HCV transmission from non-viremic mothers may represent misclassification of maternal viremic status, as a result of HCV RNA degradation in stored maternal serum samples³⁵ or as a result of intermittent maternal HCV viremia.³⁶ False-negative misclassification of maternal viremia could result from HCV titres below the lower limit of detection for the particular RT-PCR assay utilized. Alternatively, since HCV can infect peripheral blood mononuclear cells, HCV-RNA may be detected in whole blood of individuals whose plasma samples are PCR-negative.³⁷

Women with no detectable HCV-RNA in breast milk do not appear to transmit infection by breastfeeding, even if HCV-RNA is detectable in serum.^{15,27,30}

Is risk of postpartum MTC HCV transmission in mother-infant pairs correlated with HCV-RNA titres in maternal serum or breast milk?

Some studies suggest that MTC HCV transmission, regardless of mode of feeding, is unlikely when maternal serum HCV-RNA titres are below 10^5 to 10^6 copies/ml as measured by branched DNA or competitive PCR,^{11,12,18,32} although this is the approximate lower detection limit of some quantitative assays. Other investigators have failed to detect a clear threshold of viral titre below which transmission does not occur,^{19,20,38,39} and transmission has been documented when maternal serum HCV-RNA titre was below 10^3 copies/ml.²⁰ Overall, most studies point to an increased risk of HCV infection associated with high serum titre of HCV-RNA in the mother,^{11,12,14,27,32,40,41} but the correlation is not absolute.

Higher rates of transmission have also been associated with maternal and/or infant HIV infection regardless of feeding method.^{11,12,14,16,38,42} Co-infection with HIV in HCV-infected mothers has been associated with increased maternal HCV-RNA titres, which may explain the increased efficiency of MTC HCV transmission.^{8,14}

One study of 65 breastfeeding, asymptomatic, HCV-infected mothers and their infants found a correlation between maternal breast milk HCV-RNA titre and risk of MTC HCV infection.²⁷ HCV-RNA was detected in the serum, colostrum supernatant and colostrum precipitate of all 65 mothers, but in none of their infants, in the early neonatal period. Five mothers developed symptomatic liver disease by 3 months post-partum, accompanied by significant increases in HCV-RNA titres in maternal serum and breast milk. All 5 mothers continued breastfeeding during their illness. By 5 to 6 months age, 3 of the 5 infants born to these symptomatic mothers (all by elective Caesarian section) developed clinical and laboratory confirmed acute viral hepatitis, with newly detectable serum HCV-RNA. Intrapartum MTC transmission or postpartum transmission by an unrecognized blood or body fluid exposure unrelated to breastfeeding could not be ruled out. The infants born to the 60 mothers who remained asymptomatic throughout the 12 month follow-up period remained HCV-RNA negative throughout the 12 month follow-up period.

Interpreting Evidence To-date:

Under certain circumstances, the additional risk of HCV infection due to breastfeeding appears to be so low as to be only a theoretical possibility. These circumstances include asymptomatic, HCV-seropositive, HIV-negative mothers in whom serum HCV-RNA cannot be detected. More limited evidence suggests that asymptomatic, HIV-negative mothers with detectable serum HCV-RNA below 10^5 to 10^6 copies/ml but no detectable HCV-RNA in breastmilk are also at very low risk of transmitting HCV by breastfeeding. For women who satisfy these criteria, breastfeeding can be recommended, if the mother is counseled about and accepts a theoretical risk of MTC HCV transmission by breastfeeding (see “informed decision-making” below).

Three risk factors have been associated with increased risk of HCV transmission from chronic HCV-infected mothers to their infant, irrespective of mode of feeding:

- when the mother has a high serum HCV-RNA titre (i.e. 10^6 copies/ml or higher)
- when the mother has clinical symptoms and/or signs of acute hepatitis
- when the mother is co-infected with HIV

A common biologically plausible mechanism by which these factors may increase risk of HCV transmission in breastfeeding mother-infant pairs is from increased HCV titre in breastmilk, although higher HCV titres may also increase the risk of transmission by mechanisms other than mode of feeding. In any of these circumstances, it is

reasonable to advise mothers not to breastfeed and ensure that alternative infant feeding is affordable.*

Informed Decision-making

The greatest dilemma for HCV-infected mothers will be when circumstances indicate only a theoretical risk of transmission. A decision to either breastfeed or not will represent each mother's assessment of the relative risk and benefits associated with breastfeeding. By choosing to breastfeed, a very small theoretical risk of MTC transmission of HCV is accepted in return for substantial benefits accruing from breastfeeding. By deciding not to breastfeed, risk of infant HCV infection by this specific transmission mode is avoided, but the many demonstrable benefits to mother and child associated with breastfeeding are forfeited.

...the future

A randomized controlled trial with sufficient sample size to adequately evaluate perinatal transmission co-factors and their interactions would be the most scientifically valid way to evaluate whether breastfeeding causes MTC transmission of hepatitis C. However, given the many health benefits of breastfeeding, and the increased maternal morbidity associated with such co-factors as Caesarian Section, such a study may not be justifiable on either medical or ethical grounds, unless the overall health outcomes of breastfed and formula fed infants of HCV-positive mothers are similar.

Better evidence of whether MTC HCV infection is caused by breastfeeding awaits the results of future prospective studies involving large numbers of chronic HCV-infected mothers and their infants. A formal clinical decision analysis of feeding alternatives for an HCV-infected mother and her infant would be very useful. A meta-analysis of current evidence may also be useful, although the quality of data from studies prior to about 1998 may be compromised by the unreliability of earlier HCV-RNA assays. In the meantime, perinatal care providers will continue to have an important role helping chronic HCV-infected mothers make informed decisions with respect to breastfeeding.

Appendix 1

Current Advisory Recommendations Concerning HCV infected Mothers and Breastfeeding

Canadian Public Health Consensus Statement, 1998²⁵

Breastfeeding is recommended in general because of its proven health benefits and because the risk of HCV transmission by this means is only theoretical. Women who wish to take no risk may choose to use alternative feeding methods. If the nipples are

* The British Columbia government recently announced changes to the BC Benefits program so that mothers receiving income assistance and who cannot or should not breastfeed under a doctor's recommendation, are now eligible for free infant formula for up to one year.

bleeding or cracked, it is recommended that breastfeeding be suspended until they are healed.

Infectious Diseases and Immunization Committee, Canadian Paediatric Society, 1997²²

On the basis of the limited available information, the safety of breastfeeding has not been satisfactorily established. Mothers who wish to breastfeed should be given all available information in order to make an informed decision. HIV-coinfection is a contraindication to breastfeeding.

U.S. CDC Advisory Committee on Immunization Practice and American Academy of Pediatrics, 1997²⁴

HCV RNA and antibody to HCV have been detected in milk of mothers infected with HCV. Although published data are limited, HCV transmission via breastfeeding has not been documented in anti-HCV positive, anti-HIV negative mothers. HCV-infected mothers should be counseled that transmission of HCV by breastfeeding theoretically is possible, but has not been documented. According to the US Public Health Service, maternal HCV infection is not a contraindication to breastfeeding. The decision to do so should be based on informed discussion between the mother and the health care provider.

Canadian Paediatric Society, undated statement²³

Currently, there is no evidence that the virus can be transmitted by breastfeeding. However, the studies done to date have not established clearly the safety of breastfeeding in this situation. If you are infected, the decision to breastfeed should be made in consultation with your doctor.

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