Vertical transmission of the hepatitis C virus: Current knowledge and issues

Canadian Paediatric Society

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Hepatitis C virus (HCV) is an important cause of chronic liver disease, accounting for an estimated 40% of cases in developed countries (1). Despite the introduction of an effective screening policy for all blood donations, transmission continues to occur by other means.

Soon after the discovery of HCV in 1989, both serological tests for antibody detection and a genomic amplification method (reverse transcription followed by polymerase chain reaction) for HCV RNA detection were developed. With these tools in hand, investigators began studying the epidemiology, pathogenesis and natural history of HCV infection. Investigators were quick to observe that HCV infections had features similar to those of other blood-borne infections, and early on raised the possibility of vertical transmission of HCV, a well-established characteristic of both hepatitis B virus and HIV. Studies have since shown that HCV is transmissible from the infected mother to her offspring, which raises a number of issues that will be dealt with in the present statement. It replaces the previous position statement published in 1997 (2).

EPIDEMIOLOGY OF HCV INFECTION

HCV is thought to infect between 1% and 3% of the adult Canadian population, but the true incidence is difficult to establish because the majority of infected people are asymptomatic and population-based seroprevalence studies have not been performed. HCV seroprevalence was 0.48% in tissue and organ donors in northern Alberta between 1998 and 2004 (3), and 2.8% in patients presenting with major trauma in London, Ontario, in 2003 (4). Inuit and First Nations people appear to have higher seroprevalence rates compared with other Canadians, but may have a lower risk of progression to chronic HCV infection (5). HCV infection was more prevalent in individuals who received transfusions before the introduction of screening of blood donations in 1990. Since the introduction of HCV testing of all blood donations in 1990, the risk of post-transfusion HCV infection has fallen precipitously. It is now estimated that a maximum of one in 2.3 million blood donations in Canada will be contaminated with HCV (6). HCV infection is highly prevalent in hemophiliacs who received untreated factor VIII concentrates and in intravenous drug users (IVDUs). Over 50% of IVDUs were seropositive in past studies (7-9); in two sentinel surveillance studies (10,11) of acute HCV infection, intravenous drug use was the major risk factor. Disappointingly, there has been no reduction in seropositivity in more recent studies of IVDUs (12), despite efforts to inform the general public about the risks of sharing needles. In many cases of chronic HCV infection, a history of having 'done' intravenous drugs only a few times in the remote past is elicited. A minority of cases are found in hemodialysis patients and health care workers who have been exposed to contaminated blood and body fluids. Transmission through household contact is yet to be proven, but there are household contacts with unexplained HCV infection. The general consensus is that sexual contact is a minor mode of transmission in Canada, and it accounts for only a small proportion of cases (10).

Among pregnant women, the reported rates of HCV seroprevalence vary by country, with there being no large Canadian studies to date. The estimated rate in the United States is 1% (13), with the Canadian rate likely being comparable. The major risk factors for seropositivity in pregnant women are previous or current intravenous drug use, being the sexual partner of an IVDU and blood transfusion before 1990. Before adolescence, the infection is now transmitted almost exclusively by perinatal exposure.

NATURAL HISTORY OF HCV INFECTIONS IN CHILDREN

Table 1 outlines the different types of HCV infections. Acute HCV infection is generally subclinical, and in symptomatic individuals, it usually runs a mild clinical course. Approximately 75% of acute cases become chronic, defined as active viral replication persisting for more than six months, as indicated by the presence of HCV RNA in blood on most or all blood specimens (14). The other 25% of cases appear to clear HCV infection, but usually have persistent HCV antibodies. Although the latter patients have no detectable viremia, adult studies show that small amounts of the virus may still be detectable in the peripheral blood mononuclear cells and liver by special techniques

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Table 1
Interpretation of hepatitis C virus (HCV) virological test results

Patient age	Born to HCV-infected mother	HCV antibodies	HCV RNA PCR	HCV RNA in liver or PBMCs*	Interpretation	Significance in paediatric patients
≤2 mo	Yes	Present	Not detected		Too early to interpret result because patient may not yet be viremic if transmission occurred at birth.	
2–17 mo	Yes	Present	Not detected		Vertical transmission of HCV did not occur, or the child has cleared HCV	Because the sensitivity of HCV RNA PCR may be <100%, antibodies should be tested at ≥18 months of age. If still present, HCV RNA PCR should be repeated to ensure HCV has been cleared. Children who clear HCV likely have no or very rare sequelae.
≥6 mo	Yes/No	Present	Detectable for >6 mo		Chronic HCV	Usually persists indefinitely in the absence of antiviral therapy, but spontaneous clearance likely more common in children than in adults.
≥18 mo	Yes/No	Present	Not detected	Small studies (15,16) in adults show virus almost always detectable in PBMCs and liver	Clearance of HCV†	Clearance occurs spontaneously with approximately 25% of acute HCV and an undetermined small percentage of chronic HCV, or occurs with successful antiviral therapy.
Any age	Yes	Absent	No need to test		Vertical transmission of HCV did not occur, or the child has cleared HCV	Children who clear HCV likely have no or very rare sequelae.
Any age	Yes/No	Present	Detectable in a child <6 mo of age, or detectable <6 mo after a negative antibody or PCR test		Acute HCV	An estimated 75% will develop chronic HCV and 25% will clear HCV.
Any age	Yes/No	Absent	Present		Seronegative (immunosilent) HCV, or very early acute HCV (infection typically occurred 20 to 60 days prior)	Seronegative HCV mainly described in HIV coinfected adults and other immunosuppressed patients with the incidence in children not known.
Any age	Yes/No	Absent	Absent	Present	Occult HCV	Described in adults with unexplained elevated transaminase levels (18), with there being no paediatric studies.

*Interpretation assumes the HCV RNA result is not a false-positive, which occurs on rare occasions. *Only available as a research tool; †Some experts label this 'occult HCV' if virus is detectable in peripheral blood mononuclear cells (PBMCs) or in the liver, and transaminases are normal; most reserve the term 'occult HCV' for seronegative patients. Mo Months; PCR Polymerase chain reaction*

performed in research laboratories (15,16). The infectivity and the incidence of sequelae of HCV infection in patients with clearance of viremia (as detected by commercial assays) is thought to be very low, but follow-up over decades will be required to definitively establish their prognosis. Spontaneous clearance of chronic HCV infection after more than six months of viremia is very unusual in adults, but was described in 12% of 50 children with elevated serum aminotransferase levels after two to five years of observation (17). A total clearance rate of 25% to 30% has been reported in a larger Canadian series (18) of 157 children, with almost all cases of clearance of vertically transmitted HCV infection occurring by seven years of age. It has recently been recognized that adults with unexplained elevations of serum aminotransferase levels may have 'occult HCV infection' with small amounts of virus detectable in the liver and peripheral blood mononuclear cells, in the absence of HCV antibodies or viremia as detected by commercial assays (19), but it is not yet clear how often this occurs in children.

The full spectrum of manifestations of chronic HCV infection during childhood is just beginning to be established. Studies (17,20,21) that included liver biopsies on children with HCV infection indicate that most children have mildly abnormal histology; gradual histological progression of disease with cirrhosis during childhood was noted in only a small percentage of children. The majority of infected children have intermittent or chronically elevated aminotransferase levels (14,20,21), with hepatomegaly being the only common physical finding (14). The correlation between aminotransferase levels and the degree of hepatitis is far from perfect, and indications for liver biopsy remain uncertain. In most studies (14,17,21), all children remain clinically well with or without treatment, but one study (20) from the United States described cirrhosis in three of 60 children or young adults (of which two required liver transplantation and one had hepatocellular carcinoma). A study (22) from Egypt described death from liver disease by 18 months of age, in six of 20 infected infants, but this dismal outcome has not been described in other studies.

HOW SHOULD HCV-POSITIVE WOMEN BE COUNSELLED ABOUT THE RISKS OF PERINATAL TRANSMISSION?

Determining the rate of vertical transmission of HCV is complicated due to inconsistent criteria for defining infection in young children. It is clear that children who are seropositive at 18 months of age or older have been infected with HCV, and that the presence of HCV RNA can be used in children 18 months of age or older to differentiate those with chronic HCV infection from those with clearance of HCV. However, classification remains controversial for infants who have HCV RNA detected in only one of multiple serial specimens and then serorevert because this may be a false-positive HCV RNA result or may mean they rapidly cleared the virus without mounting a sustained antibody response. Other children have HCV RNA detected on more than one occasion, yet ultimately are not viremic and serorevert. These children with clearance of HCV may be misclassified as not having acquired HCV in studies in which HCV RNA testing was not performed early in life. Another problem is that studies of vertical transmission are inconsistent about including women who are HCV RNA-negative because at one point it was incorrectly believed that these women never transmitted HCV to their infants.

Recognizing that different definitions are used for defining HCV infection, a review of multiple studies reveals a vertical transmission rate of approximately 5%, with the rate being lower if the mother is HCV RNA-negative (23,24). Vertical transmission has been correlated with higher maternal viral titre (13,23), an elevated alanine aminotransferase level in the year before pregnancy (25) and the presence of maternal cirrhosis (26), with there being conflicting results on the role of maternal intravenous drug use in increasing transmission (23,24). HIV coinfection is clearly a risk factor for HCV vertical transmission, with rates of approximately 25% being described in early studies. It appears that treatment of HIV with antiretrovirals may eliminate this excess risk (13,24), thus all coinfected women past the first trimester should be on antiretrovirals to reduce the risk of transmission of both HIV and HCV. The HCV genotype is not known to influence the transmission risk (23).

All women with HCV infection should also be screened for HIV and chronic hepatitis B infection.

WHAT IS THE ROLE OF MODE OF DELIVERY AND BREAST MILK IN HCV TRANSMISSION?

As with HIV, the evidence supports both intrauterine and intrapartum transmission of HCV. In some cases, viremia has been demonstrated in newborn serum (27), whereas in most reported cases, HCV-RNA was only detectable a few weeks after birth (28,29). Both concordance (30) and discordance (24,31) for HCV status have been described in twins. Although the available evidence points to the intrapartum period as the main time of transmission, the relative importance of intrauterine versus intrapartum transmission remains to be established by well-planned studies involving repeat specimens during the early newborn period.

The mode of delivery did not appear to alter the rate of HIV transmission, until a randomized study (32) was performed showing benefit from elective caesarian section, using a more rigorous definition of 'elective' (no labour and no rupture of membranes). A large European observational study (24) of HCV transmission, using this same rigorous definition, demonstrated no benefit of elective caesarian section, but unexpectedly demonstrated that infant female sex may be a risk factor. Prolonged rupture of membranes has inconsistently been demonstrated to be a risk factor for HCV transmission (13,24,33). Pending randomized trials,

the mode of delivery should not be determined by maternal HCV status. However, procedures that promote mixing of fetal and maternal blood, such as the use of scalp electrodes or amniocentesis, should be avoided because there is some evidence of risk (33); randomized trials of these interventions are not likely to be performed.

Despite the fact that HCV RNA has been detected in breast milk (33), multiple observational studies (23,24) suggest that breastfeeding does not appear to play an important role in the mother-to-infant transmission of HCV. One theory as to why transmission via breast milk never or rarely occurs is that gastric acid rapidly inactivates HCV (13). Women with HCV infection should be advised that unless there are other contraindications, they should consider breastfeeding their infants, but that it is not possible to totally exclude the possibility that HCV transmission could occur via this route. The benefits of breastfeeding outweigh the theoretical, but unproven, risk of HCV transmission to the infant. However, women who experience a flare of chronic HCV infection with jaundice postpartum or develop cracked, bleeding nipples should stop breastfeeding.

SHOULD ALL PREGNANT WOMEN BE ROUTINELY SCREENED FOR HCV INFECTION?

Unfortunately, there is no known method for preventing vertical HCV transmission. The benefits of early detection of infected children are unknown. Therefore, routine prenatal screening for HCV infection is not currently advised. However, screening of high-risk women is important because antiviral therapy can then be considered in the postpartum period and may decrease their risk of end stage liver disease and hepatocellular carcinoma. The following women should be considered high-risk (10):

- Past or present IVDUs;
- Recipients of blood products before 1990 in developed countries and/or at any time in developing countries;
- Patients with unexplained elevated aminotransferase levels; and
- Patients who have undergone organ or tissue transplantation from unscreened donors.

WHAT IS THE ROLE OF ANTIVIRAL THERAPY FOR PREGNANT HCV-INFECTED WOMEN OR INFECTED WOMEN CONTEMPLATING PREGNANCY?

Treatment of chronic HCV infection before pregnancy will lower the risk of transmission if it is successful, but is not normally advised in the absence of other indications for HCV therapy. Furthermore, reinfection is common if the risk factor for HCV acquisition is intravenous drug use. However, treatment before pregnancy might be considered in women who are currently not IVDUs and who agree to use effective birth control until they complete antiviral therapy. The efficacy of antivirals administered during pregnancy or to the infant for prevention of vertical transmission has not been studied. Ribavirin is teratogenic in animals, and its safety in newborns has not been evaluated.

WHAT IS THE PROPER MANAGEMENT OF A CHILD BORN TO AN INFECTED MOTHER?

Blood is the major source of HCV transmission. Therefore, no special precautions are necessary for the care of the newborn in the nursery because there is no known risk of transmission by saliva, urine or stool. It is important to eventually establish whether HCV was transmitted to the child to ensure medical follow-up of infected children, and to reassure the 95% of women who did not transmit HCV to their infants. Unfortunately, HCV serology is not reliable during infancy because passively transferred maternal antibody may persist for up to 18 months (12), although, one study (34) estimated that over one-half of uninfected infants will be seronegative by six months of age and 95% by 12 months of age. Therefore, serology performed at 12 to 18 months of age is the primary diagnostic test (with the test repeated at 18 months of age, if it is still positive before that age). Earlier diagnosis of HCV infection is very unlikely to alter management, but there may be significant parental anxiety about the possibility of infection, or there may be concern on the part of the health care worker that an infant will be lost to follow-up. In these situations only, a single HCV RNA test at a minimum of two months of age is recommended because it is a very sensitive and specific test (34), keeping in mind the fact that clearance of the virus can be expected to occur eventually in approximately 25% of viremic infants. If the initial HCV RNA test proves positive, then the infant will require testing for HCV RNA and aminotransferase levels every six months to determine whether chronic infection or spontaneous clearance will ensue. If the initial HCV RNA test is negative, serology should be performed at 12 to 18 months of age to confirm seroreversion. Children with clearance of HCV are not thought to require follow-up, but children with chronic HCV infection (Table 1) should be cared for in consultation with a paediatric hepatologist or gastroenterologist, or infectious diseases specialist, because antiviral therapy may be indicated.

One might consider giving hepatitis B vaccine to children born to women with HCV starting in the first month of life because these children may be at a higher risk of infection, and hepatitis B may be more severe in a patient with established HCV infection. Hepatitis A vaccine may be given for the same reasons to HCV-infected children when they reach one year of age, although a recent small study (35) suggested that hepatitis A infections may at least temporarily inhibit HCV replication in adults with chronic HCV infection.

Chronic HCV infection in children is not contagious through normal activities of daily living. Therefore, routine activities, such as daycare attendance or participation in

most sports, should not be restricted. There is no legal or ethical obligation for parents or the physician to notify school authorities or supervisors that the child has chronic HCV infection. There is a theoretical risk of transmission if contact with HCV-contaminated blood occurs during contact sports, and some guidelines recommend counselling against HCV-infected children participating in boxing or wrestling (36), but this remains controversial.

SUMMARY

- Approximately 5% of pregnant women with chronic HCV infection will transmit the virus to their infants.
- Currently, there are no specific interventions known to decrease perinatal transmission.
- The primary diagnostic test for exposed infants is HCV serology performed at 12 to 18 months of age. HCV RNA performed after two months of age is a sensitive and specific, but expensive, test. Use should be considered if there is significant parental anxiety or if there is concern that the infant will be lost to follow-up.
- Approximately 25% of infected infants will clear the virus spontaneously. The other 75% generally have only mild hepatitis throughout childhood, but they require follow-up because a small percentage will develop progressive liver disease and are at risk for hepatocellular carcinoma.

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