Mother-to-Infant Transmission of Hepatitis C Virus

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Hepatitis C virus (HCV) infection is acquired through transfusion of infected blood or blood products or through routes not related to transfusion, classified as community-acquired disease. In developed countries, the predominant transmission route of hepatitis C is changing. In childhood, hepatitis C has been largely transfusional. Since the implementation of blood product screening for HCV in 1991, the incidence of transfusional hepatitis C has dropped. As children with post-transfusional hepatitis C grow up, the prevalence of community-acquired pediatric hepatitis C will increase.[1]

The rate of mother-to-infant HCV transmission is critical to predicting the burden of HCV infection in future generations. Mother-to-infant transmission of HCV may be intrauterine, intrapartum, or postnatal. The factors that determine whether or not an infant actually becomes infected need to be identified. If they can be manipulated, they represent areas for intervention to minimize mother-to-infant transmission. This review summarizes critically the current world-wide literature focusing on the rate of mother-to-infant transmission of HCV. Improved polymerase chain reaction (PCR) methods for detection of HCV RNA and larger studies will further refine the estimate of the incidence of mother-to-infant hepatitis C.

A review of published studies of mother-to-infant transmission of HCV was performed from January 1990 to December 2000. Articles were identified by computerized literature searches of MEDLINE and EMBASE, using combinations of key and free text terms (hepatitis C, mother-to-infant disease transmission, maternal-fetal exchange, placenta, mother-to-child, mother-to-infant, infant, pregnant, pregnancy). Bibliographies from review articles were manually cross-checked to identify additional references. No language restrictions were applied.

For this review, mother-to-infant transmission of HCV was defined as persistence of serum anti-HCV antibodies in the infant beyond at least 12 months of age or detection of serum HCV RNA on at least 1 occasion. Cord blood HCV RNA results were disregarded because of the possibility of contamination with maternal blood. Only original articles with at least 10 cases of anti-HCV–positive mothers were included. Studies using first-generation enzyme-linked immunosorbent assay (ELISA) or recombinant immunoblot assay (RIBA) techniques without confirmatory PCR testing were excluded.

Spontaneous clearance of mother-to-infant HCV infection (sometimes interpreted as transient viremia) was defined as seroreversion of serum HCV RNA (detected on at least one occasion and then subsequently found to be HCV-RNA negative). This may be accompanied by elevated aminotransferases during HCV-RNA positivity and subsequent loss of serum anti-HCV.

Rates of mother-to-infant transmission were expressed as a *crude rate* as well as *weighted rate* [Crude rate = $(a_1 + a_2 + \ldots + a_x)/(n_1 + n_2 + \ldots + n_x)$; weighted rate = $(p_1 w_1 + p_2 w_2 + \ldots + p_x w_x)/(w_1 + w_2 + \ldots + w_x)$ where $i = 1 - x$ total studies, a_i = numerator of each rate, n_i = denominator of each rate, p_i = each individual rate, $q_i = 1 - p_i$, w_i = 1/variance = $n_i/p_i\ q_i$]. The crude rate simply *combines* the number of infected infants and divides this sum by the total number of mother-infant pairs studied. The advantage of the weighted rate is that the reported rate of each study is adjusted by a factor that reflects the inverse of the variance. Thus the sample size and variance of each study are incorporated into the weighted rate. Rates from studies of many mother-infant pairs will carry more weight compared with smaller studies.

Seventy-seven studies were included, published between 1992 and 2000. The number of anti-HCV–positive mother-infant pairs ranged from 10 to 1,338 per study. The articles in this review reported a total of 363 cases of mother-to-infant transmission. The majority of studies originated from Italy and Japan (Table 1). One Irish series focused on women who had received HCV-contaminated anti-D immunoglobulin. Almost all studies were prospective cohorts in design.

Several studies, excluded from review because of small numbers of patients studied, examined the role of HCV nucleotide sequences and quasispecies in isolated cases of mother-to-infant transmission rather than the actual rate of transmission.[2-15] By determining the nucleotide sequence of HCV-RNA clones from the mother and infant, the degree of genetic diversity may be calculated. The most rapidly evolving region of the HCV genome, the hypervariable region, is often compared using phylogenetic analysis (*e.g.*, neighbor joining method) to show transmission of maternal HCV to her infant. The degree of homology between two samples of HCV RNA may be quantified by nucleotide substitution rate (δ), nucleotide diversity (π, average number of nucleotide differences[6]), or intersample genetic distance (Ka/Ks, a ratio of antonymous and synonymous substitutions that serves as an index of positive selective forces at the molecular level[3,13]). These studies have shown that early on, infants have a single dominant variant whereas the mother possesses multiple variants.[9] Although the HCV strains of the infant may represent a minor but transmissible maternal strain,[5] the diversity of the infant strain begins to increase at 6 to 7 months of age.[13] The evolution of HCV strains in neonates differs from that observed in their mothers and the nucleotide substitution rate increases with age.[6,10] The detection of HCV RNA in infants as early as 24 hours of age implies *in utero* (rather than perinatal) transmission because chimps develop detectable HCV RNA 3

Abbreviations: HCV, hepatitis C virus; PCR, polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay; RIBA, recombinant immunoblot assay; HIV, human immunodeficiency virus; IVDU, intravenous drug use.

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Received February 13, 2001; accepted April 30, 2001.

L.T.F.Y. is the recipient of a Fellowship from the Canadian Institutes of Health Research/Health Canada Hepatitis C Initiative.

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0270-9139/01/3402-0002$35.00/0

doi:10.1053/jhep.2001.25885

TABLE 1. Distribution of Anti-HCV–Positive Women Studied by Country

Country (reference)	No. of Studies	No. of Anti-HCV+ Mother-Infant Pairs	No. of Infected Infants
Italy (22-28,30-32,35,37-39, 42,60,61,64,67,70,72,79-86)	29	2,429	184
Ireland (62)	1	1,338	7
Japan (33,40,45,46,51,53,54, 63,65,68,87-92)	16	1,053	61
Germany (57,74,93)	3	281	10
Australia (18,19)	2	244	9
USA (20,36,94)	3	208	16
USA/Mexico (44)	1	155	13
Egypt (50)	2	167	7
Spain (34,43,48,95)	4	183	21
Sweden (66,96)	2	139	2
UK (17,97)	2	69	2
United Arab Emirates (55)	1	65	20
France (98-101)	4	64	0
Tanzania (58)	1	49	1
Taiwan (56,71,102)	3	41	3
New Zealand (52)	1	30	2
Israel (41)	1	22	4
Greece (73)	1	22	1

to 4 days post-inoculation.[9] While analysis of the hypervariable region reflects more recent changes in diversity, analysis of a more conserved region, NS5B, may provide information on more distant events. The sequence of NS5B may be determined using direct sequencing without laborious cloning, thus providing a feasible alternative for diagnosing maternal-infant transmission.[11]

The quality of the studies was largely influenced by the number of mother-infant pairs studied (sample size), the definition of mother-to-infant transmission, the frequency and duration of infant follow-up, and the method of virologic testing. All studies were of cohort design (grade "C" evidence by Guyatt et al.[16] guidelines).

PREVALENCE OF HEPATITIS C IN PREGNANT WOMEN

The prevalence of anti-HCV–positive women among all pregnant women varied widely across these studies (0.6%-95.4%, mean = 10.3%, SD = 21.9%), reflecting the heterogeneity of the populations studied. For example, the 3 studies with highest prevalence (70.1%-95.4%) were limited to intravenous drug users.[17-19] Of anti-HCV–positive women, 26.8% to 94.4% tested positive for HCV RNA (mean = 65.5%, SD = 14.6%).

For inclusion into this review, mother-to-infant transmission of HCV was defined as persistence of anti-HCV in the infant beyond at least 12 months of age or detection of serum HCV RNA on at least 1 occasion before 18 months of age. The majority of studies demanded at least one positive HCV RNA result. Some studies required more rigorous definitions of mother-to-infant transmission such as detection of anti-HCV in the infant beyond 18 months of age, detection of HCV RNA after 6 months of age, detection of HCV RNA on at least 2 occasions, elevated serum aminotransferases, or matching genotype between mother and child.

RATE OF MOTHER-TO-INFANT TRANSMISSION

The reported rate of mother-to-infant HCV transmission ranged from 0% to 35.3% among children born to anti-HCV–positive women. The crude rate among anti-HCV–positive women was 5.6% (SD = 0.3%). When adjusted by the inverse of the variance for each measured rate, the weighted rate was 1.7% (Table 2).

Among these studies, only one case of mother-to-infant transmission was reported from a woman who was negative for HCV RNA.[20] When limited to viremic women, the rate of mother-to-infant transmission ranged from 0% to 100%, reflecting the heterogeneity of populations studied. The weighted rate of mother-to-infant transmission among HCV-RNA–positive women was 4.3% (crude rate 8.1%, SD = 0.5%).

HCV transmission patterns may differ among certain groups.[21] The weighted rate for anti-HCV–positive women in Italian, Japanese, and other studies was 5.0%, 3.6%, and 1.0%, respectively. The weighted rate of mother-to-infant transmission among viremic women in Italian, Japanese, and other studies was 5.6%, 6.9%, and 3.1%, respectively. Study design was comparable among Italian, Japanese, and other studies.

The definition of mother-to-infant transmission differed among studies. When all studies were grouped according to the rigorousness of definition of mother-to-infant transmission (defined as two or more positive RNA, one or more positive RNA, or no positive RNA requirement), the weighted rates of mother-to-infant transmission among anti-HCV–positive women were 7.1% for studies requiring 2 or more positive RNA tests, 3.9% for studies requiring 1 or more positive RNA tests, and 0.6% for those with no requirement for a positive RNA test.

HUMAN IMMUNODEFICIENCY VIRUS COINFECTION

The rate of mother-to-infant HCV transmission appears increased among women coinfected with human immunodeficiency virus (HIV) compared with women without HIV infection. Based on 8 studies that included data in both

TABLE 2. Rates of Mother-to-Infant HCV Transmission Among Different Subgroups

	Mother-to-Infant HCV Transmission Rate		Used to Calculate Weighted Rate	
	Crude Rate % (SD)	Weighted Rate % (SD)	No. of Studies	No. of Mother-Infant Pairs
Anti-HCV+ women	5.6 (0.3)	1.7 (0.2)	63	5,798
Italian	7.6 (0.5)	5.0 (0.4)	26	2,324
Japanese	5.4 (0.7)	3.6 (0.6)	13	743
Other	4.1 (0.4)	1.0 (0.2)	24	2,731
RNA+ ≥ 2	9.3 (0.8)	7.1 (0.7)	20	1,324
RNA+ ≥ 1	5.8 (0.4)	3.8 (0.3)	36	2,732
No RNA in definition	1.9 (0.3)	0.6 (0.2)	6	1,591
Viremic women	8.1 (0.5)	4.3 (0.3)	53	3,184
Italian	7.8 (0.7)	5.6 (0.6)	23	1,447
Japanese	12.3 (1.5)	6.9 (1.1)	13	469
Other	6.9 (0.7)	3.1 (0.5)	20	1,321
HIV-coinfected women	22.1 (2.1)	19.4 (2.0)	8	399
HIV-negative women	4.3 (0.8)	3.5 (0.7)	8	671
IVDU	10.8 (1.9)	8.6 (1.7)	6	260
Non-IVDU	4.2 (1.1)	3.4 (1.0)	6	335
Vaginal delivery	6.7 (0.7)	4.3 (0.6)	11	1,276
Cesarean delivery	6.8 (1.2)	3.0 (0.8)	11	457
Breastfed	6.0 (1.1)	3.7 (0.8)	10	499
Not breastfed	6.3 (0.8)	3.9 (0.7)	10	862

HIV-positive and HIV-negative women, the crude rate of mother-to-infant transmission was 22.1% (SD = 2.1%) and 4.3% (SD = 0.8%), respectively. The weighted rate of mother-to-infant transmission was 19.4% and 3.5%, respectively.[20,22-28]

INTRAVENOUS DRUG USE

Patients reporting intravenous drug use (IVDU) have a high prevalence of chronic hepatitis C.[29] Studies of mother-to-infant transmission among intravenous drug users and nonusers suggest that IVDU correlates with an increased risk of mother-to-infant HCV transmission. In 6 studies that included data on women with IVDU and without IVDU, the crude rate of mother-to-infant transmission among children born to anti-HCV–positive women with IVDU was 10.8% (SD = 1.9%). The weighted rate was 8.6%. The corresponding crude and weighted mother-to-infant transmission rates for women who did not report a history of IVDU was 4.2% (SD = 1.1%) and 3.4%, respectively.[20,25,27,30-32]

MATERNAL VIRAL TITER

A correlation exists between higher maternal titers of HCV RNA and the probability of mother-to-infant transmission. Although mother-to-infant transmission occurred across a wide range of maternal viral titers, in 9 studies statistically higher maternal viral titers corresponded to a greater tendency for mother-to-infant transmission[19,33,34,40,42-46]; in 9 studies there was no difference.[18,20,27,35-39,41] Most studies reported mother-to-infant transmission at viral titers beyond the range of 10^5 to 10^6 copies/mL. In one study higher levels of maternal serum HCV RNA also tended to correlate with higher colostrum levels of HCV RNA.[47]

The timing at which serum was collected for determination of maternal viral titer was reported with variable precision. Although most studies described blood collection at or near delivery, others ranged from the third trimester to after delivery. In 5 studies, including several in which maternal titer of HCV RNA was reported as having no bearing on rate of transmission, the timing of serum collection was unclear.[18,33,41-43,45]

MODE OF DELIVERY

The mode of delivery was evaluated as a risk factor for mother-to-infant transmission in 11 studies.[24-26,34-38,44,48,49] Between infants delivered vaginally versus by Cesarean section, overall rates of mother-to-infant transmission were similar. For vaginal delivery and Cesarean section respectively, the weighted rate of mother-to-infant transmission was 4.3% and 3.0% (crude rate 6.7%, SD = 0.7% and 6.8%, SD = 1.2% respectively). Although Cesarean section was not further classified as elective or emergency, one study suggested an increased likelihood of mother-to-infant transmission with longer duration of membrane rupture.[19]

BREAST FEEDING

The role of breast feeding was evaluated as a risk factor for mother-to-infant transmission of HCV in 10 studies.[24-27,31,34,35,38,40,48] Only one of these studies defined the extent (duration and exclusivity) of breast feeding.[24] Overall rates of mother-to-infant transmission between breast-fed and non–breast-fed infants were similar. The weighted rate of mother-to-infant transmission was 3.7% and 3.9% for breast-fed and non-breast-fed infants, respectively (crude rate 6.0%, SD = 1.1% and 6.3%, SD = 0.8% for breast-fed and non-breast-fed infants, respectively). Although some investigators have detected HCV RNA in breast milk, no definite case of mother-to-infant transmission of HCV via breast milk has been reported.

GENOTYPE

Viral genotype was reported infrequently in 32 studies.[17,19,20,23,25,27,28,33-35,37,38,40,41,45,46,50-65] In most cases, only the genotypes of vertically infected babies were noted. No conclusion could be drawn as to the effect of genotype on rate of mother-to-infant transmission.

OUTCOME OF INFANTS

Inconsistent follow-up among studies resulted in only sporadic description of clinical outcome for infected infants. No symptoms of liver disease were reported in the majority of case series; this may be an underestimate because many studies focused on the rate of transmission rather than the long-term outcome. However, in one Egyptian study of 20 HCV-RNA–positive infants, 4 died of severe liver disease by 6 months of age. The remaining 16 infants were chronically sick with liver disease. Only 9 of these 16 infants later became asymptomatic despite remaining chronically infected.[55] It is uncertain why these Egyptian infants were much sicker than other affected infants of HCV-infected women.

Among studies describing mother-to-infant transmission rates, liver histology was described in only 17 infants. The reported age at time of liver biopsy ranged from 9 months to 5.5 years.[23,46,66] The majority of liver biopsies revealed changes consistent with chronic hepatitis. Fibrosis on liver biopsy was described in 3 cases.[67] One infant was successfully treated with interferon alfa.[25] Three of the 17 infants died[36]; 1 of these was coinfected with HIV[27] whereas another received 6 months of parenteral nutrition.[26]

Spontaneous loss of serum HCV RNA, interpreted as either clearance of mother-to-infant HCV infection or transient viremia, was suggested in 59 cases.[17,18,25,28,34,38,41-43,52,57,66,68-73] In these infants, serum HCV RNA was detected on at least one occasion and then the infant was subsequently found to be HCV-RNA negative. Many of these infants subsequently cleared serum anti-HCV. Six of these infants had elevated aminotransferases during the period of serum HCV-RNA positivity.[19,28,63,65]

Passive transfer of maternal antibody accounted for a majority of infants born to women with hepatitis C. The gradual loss of serum anti-HCV in infants occurred by 18 months of age in the vast majority of cases, and many lost anti-HCV earlier, by 12 months of age. Of the 45 studies that described time to clearance of anti-HCV, there were only 3 outlying cases described, in whom clearance of anti-HCV occurred between 20 and 24 months of age.[32,35,74]

Taken altogether, the studies included in this review estimate the rate of mother-to-infant transmission in the range of 1.0% to 5.0% in anti-HCV–positive women. A higher rate of mother-to-infant transmission (3.1% to 6.9%) applies if the denominator is restricted to HCV-RNA–viremic women. The majority of data is derived from Italian and Japanese studies. Rates of mother-to-infant transmission may differ in other parts of the world, because Japanese and Italian studies tend to have higher rates of mother-to-infant transmission compared with other studies. Although combined data from other countries have generally found lower estimates of mother-to-infant

transmission, the unusually severe clinical outcome of vertically infected infants from Egypt emphasizes the heterogeneity of HCV disease.

Several factors have been proposed as determinants in mother-to-infant HCV transmission, including maternal coinfection with HIV, IVDU, maternal viral titer, mode of delivery, breast feeding, and viral characteristics (*e.g.*, genotype). In this summary, women coinfected with HIV or those who report a history of IVDU tended to have a higher rate of mother-to-infant transmission compared with those without such cofactors. By contrast, mode of delivery and prevalence of breast feeding did not significantly influence rates of mother-to-infant transmission. Suggested viral factors such as genotype and viral titer were not consistently measured across studies; their roles as significant risk factors in mother-to-infant transmission remain to be conclusively shown.

It is important to define mother-to-infant HCV transmission clearly. The requirement of detectable anti-HCV in the infant beyond 12 months of age or serum HCV RNA on at least one occasion appears reasonable. When more rigorous criteria are applied (such as detection of HCV RNA on more than one occasion), studies that required at least 2 positive HCV-RNA results had higher rates of mother-to-infant transmission than studies that required fewer HCV-RNA results. Such results contradict the expectation that a more rigorous definition of mother-to-infant transmission would yield a lower rate of mother-to-infant transmission. Definition of mother-to-infant transmission alone fails to explain the heterogeneity of mother-to-infant transmission rates. Studies with more rigorous definitions may have been more complete in other aspects, including more complete follow-up, more frequent monitoring of blood work, and more meticulous laboratory methods.

A larger study will provide a more precise measure of the mother-to-infant transmission rate compared with a smaller study. To address this problem of different sample size and variance among studies, a weighted rate of mother-to-infant transmission was determined. The weighted rate is robust; in smaller studies (of less than 100 mother-infant pairs) the transmission rate was 9.9% (SD = 0.6%) whereas the weighted rate of 4.6% (SD = 0.4%) remained within the range of 1% to 5%. Such weighting may help explain why more recent, larger studies reported a lower rate of mother-to-infant transmission compared with earlier studies of smaller size. As well, the denominator of the transmission rate must be specified. Most studies use "anti-HCV–positive women" as the denominator. Yet the vast majority of mother-to-infant transmission occurs from viremic mothers. If the denominator is limited to HCV-RNA–positive women, then the rate of mother-to-infant transmission is increased. Differences in mother-to-infant transmission rates among studies may be caused by variations in sample size, timing of testing, measurement technique, and definition of risk factors. Each of these aspects demands specific consideration when interpreting available data on mother-to-infant transmission or planning a future prospective study.

The duration of follow-up, timing, and frequency of testing may also influence results. The studies ranged from 0 to 23 years of follow-up and varied in the number of times HCV-RNA testing was performed per infant. Some mother-infant pairs (such as those with significant IVDU) may be less likely to be enrolled into such studies and assessed in follow-up. The diminishing number of infants evaluated over time in the large Italian study[38] emphasizes this inherent selection bias. Infrequent blood testing limited the ability to estimate the precise age at which seroreversion occurred; reluctance for more frequent blood testing remains a valid ethical concern, particularly in pediatric research. Most viremic cases were tested early (before 3 months of age), favoring early neonatal or intrauterine infection. The significance of very early testing remains to be elucidated. One recent study noted that early presence (at day 2 of life) of serum HCV RNA may disappear by 6 months of age.[41] Although the differentiation of spontaneous clearance or transient viremia in infants may not be clinically significant, this disappearance of serum HCV RNA may be underestimated if testing is delayed.

Some of the variability in test results may be related to measurement techniques. To address the high rate of false-negative and false-positive results of earlier studies, reliance on first-generation ELISA testing for anti-HCV was a criterion for study exclusion. Although second- and third-generation ELISA tests (with confirmatory RIBA testing) and reverse transcriptase PCR testing for HCV RNA are considered far more reliable, false-positive and false-negative results remain possible. Methods of measuring viral titer have different lower limits of detection.

Furthermore, the suspected risk factors for mother-to-infant transmission deserve clarification. Some patients may not report a history of IVDU. Alternatively, some physicians may not probe carefully enough for a history of IVDU. Rather than mode of delivery, the extent of maternal-fetal blood exchange at time of delivery may be the major determinant of transmission as suggested by the duration of membrane rupture.[19] Similarly, the definition of breast feeding remains ambiguous: a spectrum exists between being *exclusively* and *never* fed breast milk. Although maternal viral titer may serve as a useful risk factor, the timing of measurement for each woman relative to delivery should be specified. For maternal viral titer to become adopted as a prognostic factor in mother-to-infant HCV transmission, its timing will require standardization.

Finally, the diagnosis of HCV infection in infancy may be susceptible to certain caveats: anti-HCV may represent passively transferred maternal antibody, HCV RNA may be intermittently positive (and depend on the lower limit of detection), and aminotransferases may or may not be elevated. No reliable relationship has been established between positive HCV serology and severity of liver pathology.

Thus far, the outcome of most infants with chronic hepatitis C acquired through mother-to-infant transmission appears mild. Most such children were asymptomatic. However, in the few infants who underwent liver biopsy, most had evidence of chronic hepatitis.[23,25-27,36,46,66,67] The progression of liver disease for these children remains to be assessed. Fibrosis has been documented, even in asymptomatic infants.

The phenomenon of spontaneous clearance or transient viremia was described in 17% (59 of 351) of all reported cases of mother-to-infant transmission. This matches a 17% rate of spontaneous clearance in 104 children with mother-to-infant hepatitis C[75] and remains comparable with a 30% rate of spontaneous clearance in a pediatric cohort of transfusional hepatitis C.[76,77] By contrast, in 320 adults with chronic HCV infection, only 2% showed a loss of HCV RNA over a follow-up of at least 3 years.[78] Infants may spontaneously clear HCV RNA more frequently than adults. Further study of the determi-

nants influencing whether or not chronic hepatitis C acquired by mother-to-infant transmission persists may illuminate the immune mechanisms required in overcoming HCV infection.

The overall weighted rate of mother-to-infant HCV transmission is in the range of 1.0% to 5.0%. Based on observational data from 77 cohort studies, maternal risk factors for increased mother-to-infant transmission include coinfection with HIV, history of IVDU, and maternal viremia greater than 10^6 copies/mL. By contrast, mode of delivery and breast feeding do not influence rates of mother-to-infant transmission significantly. Increased consideration of the clinical confounders and methodologic limitations has helped to narrow estimates of the mother-to-infant transmission rate of HCV substantially. Nevertheless, an estimated 170 million people worldwide are chronically infected with HCV. If 35% of these are women of child-bearing age, given an annual fertility rate of 2%, then conservative estimates suggest that 10,000 to 60,000 newborn babies will be infected with HCV each year.

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