

Hepatitis C Virus Infection in the Mothers and Infants Cohort Study

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ABSTRACT. *Objectives.* To estimate the hepatitis C virus (HCV) vertical transmission rate, the effect of potential risk factors, and the pattern of HCV antibody response and viremia in HCV-infected infants.

Study Design. The Mothers and Infants Cohort Study enrolled both human immunodeficiency virus (HIV)-seropositive and HIV-seronegative pregnant women at five obstetric clinics in New York City in a prospective cohort study between January 1986 and January 1991. HCV-infected mothers and their 122 offspring were followed-up for a minimum of 12 months for evidence of HCV infection as determined by persistent HCV antibodies or detection of HCV RNA by reverse transcription polymerase chain reaction. Comparisons among groups for categorical variables were performed using the Fisher's exact test.

Results. Seven (6%; 95% confidence interval, 2%-11%) of the 122 infants were HCV-infected. There was a tendency for increased risk of transmission with maternal viral and obstetrical factors, such as coinfection with HIV (7% vs 4%), high HIV viral load (13% vs 6%), HCV viremia (8% vs 3%), vaginal delivery (6% vs 0%), and female gender of offspring (8% vs 3%), although none of the associations reached statistical significance. After loss of maternal antibody, HCV antibody seroconversion occurred at a mean age of 26 months in 3 HIV-coinfected infants compared with 7 months of age in 4 HCV-infected HIV-uninfected infants. Serial samples showed that HCV RNA persisted in 6 infants for at least 18 to 54 months.

Conclusions. Our study is in accordance with other studies that have shown low overall HCV vertical transmission risk and a trend toward higher risk with maternal risk factors such as HIV-coinfection or HCV viremia. A delay in infant HCV antibody response may be associated with HIV coinfection although larger studies are needed to confirm these findings. *Pediatrics* 1998;102:355-359; hepatitis C virus, human immunodeficiency virus, vertical transmission, children.

ABBREVIATIONS. HCV, hepatitis C virus; HIV, human immunodeficiency virus; EIA, enzyme immunoassay; RIBA, recombinant immunoblot assay; RT-PCR, reverse transcription polymerase chain reaction; IVIG, intravenous immunoglobulin.

Cloning of the hepatitis C virus (HCV) by Choo et al¹ in 1989 and subsequent development of diagnostic assays revealed that this agent was responsible for the majority of transfusion-transmitted hepatitis cases.^{2,3} Furthermore, the vast majority of adults who develop acute HCV infection remain persistently infected⁴ with approximately one-quarter progressing to cirrhosis and perhaps one-quarter of these developing hepatocellular carcinoma.^{5,6} Although direct percutaneous inoculation is the most efficient mode of transmission of HCV, several studies have demonstrated that sexual, household, occupational, and vertical transmission of HCV may also occur.⁷⁻⁹ Reports of mother-to-infant transmission have shown that rates are highly variable (range, 0%-36%)¹⁰⁻¹³ with higher rates documented if mothers are human immunodeficiency virus (HIV) coinfecting or have HCV RNA titers >1 million copies per milliliter.^{10,11,13,14} In one study, the HCV vertical transmission rate was significantly higher for vaginally delivered infants compared with infants delivered by cesarean section.¹³ Breastfeeding is thought to play a minor role in HCV transmission.^{11,15-17}

Evaluating the risk of HCV vertical transmission has been limited by methodologic issues such as small sample size, inadequate duration of follow-up, variable types of serologic assays, and the lack of consensus laboratory criteria to define pediatric HCV infection.¹⁸ In the present investigation we had three major objectives: 1) to prospectively evaluate infants born to HCV-infected pregnant women with or without HIV coinfection for evidence of HCV infection, 2) to assess the effect of potential risk factors on the risk of HCV vertical transmission, and 3) to determine the pattern of HCV antibody response and viremia in HCV-infected infants.

METHODS

Between 1986 and 1991, the Mothers and Infants Cohort Study enrolled HIV-seropositive and HIV-seronegative pregnant women from five obstetric clinics in Brooklyn and the Bronx, New York, and followed their children for up to 4 years. Procedures have been reported elsewhere in detail.¹⁹⁻²¹ Briefly, after pretest counseling and informed consent, each woman was tested for HIV antibodies. All HIV-seropositive women and a set of HIV-seronegative women matched for age, ethnicity, month of gestation, and HIV transmission categories were enrolled for prospective

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evaluation. Detailed demographic, clinical data, and at most time points blood samples were collected at enrollment, during the third trimester, at delivery, and at predetermined intervals thereafter. Infants were seen monthly through age 6 months, every 3 months through age 18 months, and at 6-month intervals thereafter until 4 years of age.

For the current analysis, a maternal third-trimester blood sample and selected infant samples between 1 month and 4 years of age were screened for anti-HCV antibodies with second or third generation enzyme immunoassays (EIA 2.0 or EIA 3.0; Ortho Diagnostic Systems, Raritan, NJ). Women with nonreactive sera were considered HCV-uninfected. EIA-reactive sera were tested using a supplemental assay, ie, second or third generation recombinant immunoblot assays (RIBA 2.0 or RIBA 3.0; Chiron, Emeryville, CA). These detected antibodies against core antigen (c-22) and nonstructural proteins (c-33c, c100-c, and either c-511 or NS5). All HCV-seropositive women and infants (by EIA and RIBA) were also tested for HCV viremia by the reverse transcription polymerase chain reaction (RT-PCR) technique (HCV Amplicor; Roche Molecular Systems, Nutley, NJ). Quantification of HCV viremia was accomplished in most samples by second-generation branched DNA signal-amplification technology (Chiron Hep C bDNA 2.0). Peripheral blood HIV-1 RNA levels were determined by using the Amplicor HIV Monitor assay (Roche Molecular Systems, Branchburg, NJ). HCV genotyping was performed with a line probe assay (LiPA, Innogenetics, Brussels, Belgium). All samples were coded, frozen within 24 hours of collection, and stored at -70°C . Samples were not exposed to repeat freeze-thawing procedures.

Infants were considered HCV-seropositive when serum or plasma reacted with at least two HCV-specific antigens by RIBA 2.0 or 3.0, indeterminate when it reacted with only one, and negative when it did not react with any HCV-specific antigens. HCV-infected infants were defined as: 1) HCV antibody positive at or after 18 months of age, or 2) HCV RNA positive on two or more separate occasions. Infants who were HCV antibody negative at or after 18 months of age or were HCV RNA negative after age 6 months were considered HCV-uninfected (the cutoff of 6 months was used because a significant proportion of HCV-infected infants may remain PCR negative for the first 3 to 6 months of life²²). Infants were classified as probably uninfected ($n = 7$) if they had EIA antibody-negative test results at or after 12 months of age without a supplemental RIBA or a confirmatory HCV RNA test. For the purpose of this analysis, probably-uninfected infants were grouped with HCV-uninfected infants.

We examined the association between the risk of HCV vertical transmission and maternal viral and nonviral factors, such as maternal age, ethnicity, intravenous drug use, HIV coinfection, HIV RNA level, prenatal CD4 level, and HCV viremia using the Fisher's exact test. Only infants who were followed-up for a minimum of 12 months are included in our analyses.

RESULTS

Population Characteristics

One hundred forty-seven (41%) of 357 enrolled pregnant women were anti-HCV positive by EIA and RIBA. Seventy-nine percent of the HCV-seropositive women had currently or previously used intravenous drugs compared with 3% of the HCV-seronegative women ($P = .001$). One hundred fifty-one infants, including four twin pairs, were born to HCV-

seropositive women. Of these, 122 infants were followed-up for a minimum of 12 months.

Seven of the 122 infants born to HCV-seropositive women were HCV infected by the end of follow-up (Table 1), giving an overall vertical transmission rate of 6% (95% CI = 2%-11%). All 7 infants were singletons. There were no infants with clinical manifestations of hepatitis during follow-up. HIV coinfection was observed in 3 infants (A to C). Of note, infant A received approximately 25 doses of intravenous immunoglobulin starting at 12 months of age (April 1989).²³ In addition, 2 infants (B and C) had a history of receiving blood transfusions: infant B was transfused at 16.5 months of age (March 1992), seroconverted at 18 months of age, and first tested positive for HCV RNA at 23 months of age; infant C was transfused at birth (March 1986), and HCV RNA was positive at the first sampling time of 8 months of age. Among 115 singleton HCV-uninfected infants, passively acquired HCV antibodies were lost at a median age of 6 months (range, 1-18 months) as detected by EIA.

Nonviral Risks Factors for Vertical Transmission

Older maternal age at delivery, intravenous drug use during pregnancy, breastfeeding, and female gender of infant showed an increase in risk of HCV vertical transmission; however, none of these associations reached statistical significance (Table 2). Six of 7 HCV-infected infants were delivered vaginally. The risk of HCV transmission was higher for vaginally-delivered than for cesarean-delivered infants, but this association also did not reach statistical significance (6% vs 0%; $P = .6$).

Viral Factors

HCV RNA as detected by RT-PCR or bDNA was found in 72 (69%) of the 104 HCV-seropositive mothers with adequate samples. The median third-trimester RNA titer in mothers of infants infected with HCV was 3.7×10^6 eq/mL (range, 1.7×10^6 to 4.8×10^7 eq/mL) compared with a median HCV RNA titer of 4.2×10^6 eq/mL (range, 1.1×10^6 to 1.6×10^7 eq/mL) in mothers who did not transmit HCV to their infants.

There was no statistically significant difference in detection of HCV viremia between mothers with HCV alone and those coinfecting with HIV [25 of 49 (51%) vs 47 of 73 (64%), $P = .2$]. There was a trend toward increased risk of vertical transmission with maternal HCV viremia, but this was not statistically significant (8% vs 3%, $P = .4$). Of the mothers with

TABLE 1. Prevalence of Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) in 122 Infants of HCV-Infected Women

Mothers	Infants		Total
	HCV+HIV+	HCV+HIV-	
HCV+HIV+	3 (A-C)*	2 (F-G)	73
HCV+HIV-	0	2 (D-E)	49
Total			122

* For comparison with text and Fig 1, the HCV-infected infants are labeled A-G. The three infants also infected with HIV (A-C) are indicated in bold.

TABLE 2. Nonviral Risk Factors for Vertical Transmission of Hepatitis C Virus

Factor	No. of Infants Studied*	No. of Infants HCV-Infected (%)	P Value
Maternal age at delivery, y	122		
18–26	28	1 (4)	.8 Trend .5
27–32	54	3 (6)	
33–45	40	3 (8)	
Ethnic group	122		
White	20	2 (10)	.6
Black	48	2 (4)	
Hispanic	54	3 (6)	
Ever IV drug use	116		
No	23	1 (4)	1.0
Yes	93	5 (5)	
IV drug use during pregnancy	122		
No	64	3 (5)	.7
Yes	58	4 (7)	
Mode of delivery†	115		
Vaginal	94	6 (6)	.6
Cesarean	21	0 (0)	
Breastfeeding	122		
No	114	7 (6)	1.0
Yes	8	0 (0)	
Infant's gender	122		
Male	62	2 (3)	.3
Female	60	5 (8)	

* Numbers do not always total 122 due to missing data.

† Seven infants had unknown mode of delivery.

HCV viremia, the risk of vertical transmission was high whether the mother was coinfecting with HIV (4 of 47, 9%) or had HCV alone (2 of 25, 8%). In the absence of detectable maternal HCV viremia, the transmission rates were 5% (1 of 21) with maternal HIV infection and 0% (0 of 11) without maternal HIV infection.

HIV RNA levels were determined on 59 of 73 mothers coinfecting with HIV (Table 3): 13% (3/23) of infants born to women with third-trimester HIV-RNA levels $\geq 10\,000$ copies/mL were infected with HCV compared with 6% (2/36) of infants born to women whose HIV RNA level was $< 10\,000$ copies/mL ($P = .4$).

Mother-infant pairs showed homology with respect to HCV major genotype 1 (subtypes 1a or 1b) in 4 out of 5 pairs (80%). The exception was infant D,

TABLE 3. Viral Risk Factors for Vertical Transmission of Hepatitis C

Factor	No. of Infants Studied	No. of Infants HCV-Infected (%)	P Value
HIV coinfection	122		
No	49	2 (4)	.7
Yes	73	5 (7)	
CD4+ prenatal level	106		
$< 20\%$	11	1 (9)	.5
$\geq 20\%$	95	5 (5)	
HIV RNA level	59		
$\geq 10\,000$ copies/mL	23	3 (13)	.4
$< 10\,000$ copies/mL	36	2 (6)	
HCV RNA positive	104		
No	32	1 (3)	.4
Yes	72	6 (8)	

who had subtype 4c/4d, whereas the mother had subtype 1b on two separate samples. HCV genotyping was unsuccessful in 2 infants (A and B).

Patterns of Antibody Response and Viremia in Children

Patterns of HCV antibody responses and HCV viremia in HCV-infected children were highly variable (Fig 1). Infant A lost maternal antibodies by 6 months of age, seroconverted at 24 months of age, and remained antibody positive throughout the follow-up period; however, he never tested positive for HCV viremia. Infant B lost maternal antibodies by 6 months, seroconverted between 15 and 18 months of age, and tested positive for HCV RNA at 23 months of age, the first sample tested by RT-PCR. Infant C lost maternal antibodies by 9 months, had an isolated c33c antibody band until age 36 months, and had persistent viremia on all but the neonatal/pretransfusion sample. Infants D and F did not have antibody tests until 7 months of age. In infants E and G there was nearly complete loss of maternal antibodies, followed by seroconversion between 6 and 9 months of age. Thus, the 4 HIV-uninfected infants (D to G) seroconverted at much younger ages (range, 5–7 months) than the 3 HIV-coinfecting infants (A to C; range, 18 to 36 months).

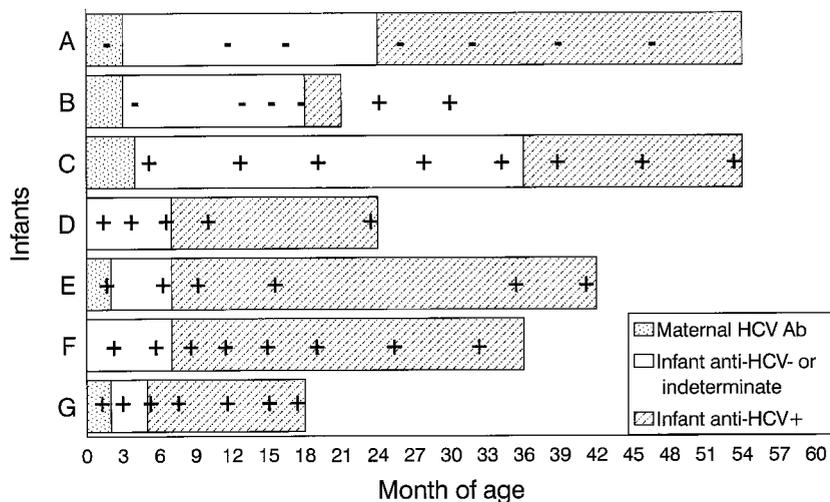
Viremia persisted in 6 of 7 infants (B to G) for at least 18 to 54 months. After age 6 months, HCV RNA titers were relatively stable and were highest in infant C (22×10^6 eq/mL), intermediate in infants B, D, and F (6 to 10×10^6 eq/mL), and lowest in infant E (3×10^6 eq/mL).

DISCUSSION

Our findings confirm mother-to-infant transmission of HCV in inner city women with a high prevalence of intravenous drug-abusing behavior. In accordance with other studies, overall vertical transmission rate was low, 6%. Three infants (A to C) may have been at additional risk of HCV infection after postnatal exposure to blood or blood products. However, Gammaguard (Baxter Healthcare Corporation, Deerfield, IL) intravenous immunoglobulin (IVIG) was found to be the only IVIG product implicated in transmission of HCV in a large cohort of children who received IVIG for immunodeficiencies²³ and infant A, who was coinfecting with HIV, received Gammamune (Bayer Corporation, Westhaven, CT) IVIG. Infant B was transfused with packed red blood cells in 1992, after the introduction of universal donor HCV screening, and infant C had an identical subtype as his mother (1a) on two separate occasions. One mother-infant pair (D) in our study had mismatched major genotypes. Mislabeling or contamination of samples could explain this discrepancy. It is also possible that the mother was infected with more than one HCV genotype^{24–26} and transmitted one that was not detected by our technique.

We studied the potential role of several factors on HCV vertical transmission. In accordance with other studies, we found that transmission rates were slightly higher in the presence of concomitant HIV

Fig 1. Summary of HCV markers in HCV-infected infants. Shaded bars indicate periods of HCV-seropositivity by RIBA. Positive and negative marks indicate positive and negative results of HCV RNA tests. Infants A, B, and C were coinfecting with HIV and were exposed postnatally to blood products.



infection^{11,13} or high maternal HCV viremia.¹⁰ It has been suggested that HIV-induced immunodeficiency may promote increased HCV replication and therefore facilitate infectivity.²⁷ We noted some evidence of increased risk with high maternal HIV RNA level,²⁸ older maternal age at the time of delivery, vaginal mode of delivery, and female gender of offspring. However, because of the small numbers of HCV-infected infants, our study had low statistical power.

Thomas et al²² recently reviewed the use of HCV PCR and antibody tests in the diagnosis of vertically transmitted HCV. Data from 48 studies were systematically pooled to include a total of 74 HCV-infected and 297 HCV-uninfected children. An estimated 89% of infants with strong evidence of HCV infection were PCR positive by 3 months of age. All HCV-uninfected infants lost maternal antibody by 18 months of age. Many HCV-infected children remained antibody positive throughout the follow-up period; however, in several cases periods of transient seronegativity lasting between 3 to 12 months were reported between the ages of 2 to 24 months, similar to infants A, B, C, E, and G in our study.^{10,11,13}

In the setting of pediatric HIV infection, both HCV antibody and HCV RNA testing of serial samples were required to diagnose pediatric HCV infection, as illustrated by infants A and C, who lacked either detectable viremia or a sufficient antibody pattern. Manzini et al²⁹ demonstrated that clearance of passively acquired HCV maternal antibodies was significantly slower among infants born to HIV-infected mothers than to those born to HIV-uninfected mothers. In our study, the 3 HIV-coinfecting infants became HCV-seropositive between the ages of 18 and 36 months. Conversely, without HIV infection, HCV RNA was detected by 2 to 6 months of age, and HCV antibody seroconversion and persistence was apparent by 5 to 7 months of age in all 4 HCV-infected HIV-uninfected infants.

Natural history studies on small series of HCV-infected children demonstrate that in most children, similar to adults, there is persistent infection.³⁰⁻³³ Palomba et al³² followed 7 HCV-infected infants for a mean of 65 months and found all infants to be

viremic at the time of last analysis. Liver biopsies done on 5 of the infants were consistent with chronic persistent HCV infection.³² HCV persisted in 6 of our infants for at least 18 to 54 months. Although none of our study infants had clinical hepatic abnormalities that were sufficient to trigger a thorough evaluation, transient elevations of alanine aminotransferase (ALT) levels during infancy were reported to be common with HCV infection, occurring in ~80% of cases.³⁴ Various factors can affect the clinical evolution of chronic HCV in childhood. Outcome may be related to very young age at the time of primary infection as well as the underlying immune system of the host.³⁰ Currently there is no effective way to prevent vertical transmission. That children can be life-long reservoirs of HCV may have serious implications for controlling the spread of this infection.

CONCLUSION

HCV transmission with perinatal exposure is relatively inefficient, but seems to be slightly higher if the mother is HIV coinfecting or has HCV viremia during pregnancy. Previous studies have been limited by short duration of follow-up. With follow-up beyond 3 years of age we were able to detect late seroconversion in HIV-coinfecting infants. A multicenter collaborative study approach is clearly needed to better understand risk factors associated with vertical transmission, the natural history of perinatal HCV infection, and treatment options for children with chronic HCV infection.

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REFERENCES

1. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from bloodborne non-A, non-B viral hepatitis genome. *Science*. 1989;244:356-362
2. Alter HJ, Purcell RH, Shih JW, et al. Detection of antibody to hepatitis C virus in prospectively followed transfusion recipients with acute and chronic non-A, non-B hepatitis. *N Engl J Med*. 1989;321:1494-1500
3. Hopf U, Moller B, Stemerowicz R, et al. Long term follow up of

- posttransfusion and sporadic chronic hepatitis non-A, non-B and frequency of circulating antibodies to hepatitis C virus (HCV). *J Hepatol.* 1990;10:69–76
4. Esteban JI, Lopez-Talavera JC, Genesca J, et al. High rate of infectivity and liver disease in blood donors with antibodies to hepatitis C virus. *Ann Intern Med.* 1991;115:443–449
 5. Tong MJ, El-Farra NS, Reikes AR, Co RL. Clinical outcomes after transfusion-associated hepatitis C. *N Engl J Med.* 1995;332:1463–1466
 6. Colombo M, Romeo R. Hepatitis C infection and hepatocellular carcinoma. In: Brechot C, ed. *Primary Liver Cancer. Etiologic and Progression Factors.* London, England: CRC Press; 1994:49–55
 7. Everhart JE, Di Bisceglie AM, Murray LM, et al. Risk for non-A, non-B (type C) hepatitis through sexual or household contact with chronic carriers. *Ann Intern Med.* 1990;112:544–545
 8. Alter MJ, Hadler SC, Judson FN, et al. Risk factors for acute non-A, non-B hepatitis in the united states and association with hepatitis C virus infection. *JAMA.* 1990;264:2231–2235
 9. Kiyosawa K, Sodeyama T, Tanaka E, et al. Hepatitis C in hospital employees with needle stick injuries. *Ann Intern Med.* 1991;115:367–369
 10. Ohto H, Terazawa S, Nobuhiko S, et al. Transmission of hepatitis C virus from mothers to infants. *N Engl J Med.* 1994;330:744–750
 11. Zanetti AR, Tanzi E, Paccagnini S, et al. Mother-to-infant transmission of hepatitis C virus. *Lancet.* 1995;345:289–291
 12. Sabatino G, Ramenghi LA, di Marzio M, Pizzigallo E. Vertical transmission of hepatitis C virus: an epidemiologic study on 2980 pregnant women in Italy. *Eur J Epidemiol.* 1996;12:443–447
 13. Paccagnini S, Principi N, Massironi E, et al. Perinatal transmission and manifestation of hepatitis C virus infection in a high-risk population. *Pediatr Infect Dis J.* 1995;14:195–199
 14. Novati R, Thiers V, d'Arminio Monforte A, et al. Mother-to-child transmission of hepatitis C virus detected by nested polymerase chain reaction. *J Infect Dis.* 1992;165:720–723
 15. Lin HH, Kao JH, Hsu HY, et al. Absence of infection in breast-fed infants born to hepatitis C virus-infected mothers. *J Pediatr.* 1995;126:589–591
 16. Kage M, Ogasawara S, Kosai K, et al. Hepatitis C virus RNA present in saliva but absent in breast-milk of hepatitis C carrier mother. *J Gastroenterol Hepatol.* 1997;12:518–521
 17. Polywka S, Feucht H, Zollner B, Laufs R. Hepatitis C virus infection in pregnancy and the risk of mother-to-child transmission. *Eur J Clin Microbiol Infect Dis.* 1997;16:121–124
 18. Thomas SL, Newell ML, Peckham CS, Ades AE, Hall AJ. A review of hepatitis C virus (HCV) vertical transmission: risks of transmission to infants born to mothers with and without HCV viremia or HIV infection. *Int J Epidemiol.* 1998;27:108–117
 19. Goedert JJ, Mendez H, Drummond JE, et al. Mother-to-infant transmission of human immunodeficiency virus type 1: association with prematurity or low anti-gp120. *Lancet.* 1989;2:1351–1354
 20. Minkoff H, Burns D, Landesman S, et al. The relationship of the duration of ruptured membranes to vertical transmission of human immunodeficiency virus. *Am J Obstet Gynecol.* 1995;173:585–589
 21. Burns D, Landesman S, Muenz LR, et al. Cigarette smoking, premature rupture of membranes, and vertical transmission of HIV-1 among women with low CD4+ levels. *J Acquir Immune Defic Syndr.* 1994;7:718–726
 22. Thomas SL, Newell ML, Peckham CS, Ades AE, Hall AJ. Use of polymerase chain reaction and antibody tests in the diagnosis of mother-to-child transmission of hepatitis C virus. *Eur J Clin Microbiol.* 1997;16:711–719
 23. Bresee JS, Mast EE, Coleman PJ, et al. Hepatitis C virus infection associated with administration of intravenous immune globulin. *JAMA.* 1996;276:1563–1567
 24. Soni P, Dusheiko GM, Harrison TJ. Genetic diversity of hepatitis C virus: implications for pathogenesis. Report of a meeting of physicians and scientists, Royal Free Hospital and School of Medicine, London. *Lancet.* 1995;345:562–566
 25. Martell M, Esteban JI, Quer J, et al. Hepatitis C virus (HCV) circulates in a population of different but closely related genomes: quasispecies nature of HCV genome distribution. *J Virol.* 1992;66:3225–3229
 26. Simmonds P. Variability of hepatitis C virus. *Hepatology.* 1995;21:570–582
 27. Eyster ME, Fried MW, Di Bisceglie AM, Goedert JJ. Increasing hepatitis C virus levels in hemophiliacs: relationship to human immunodeficiency virus infection and liver disease. *Blood.* 1994;84:1020–1023
 28. Burns DN, Landesman S, Wright DJ, et al. Influence of other maternal variables on the relationship between maternal virus load and mother-to-infant transmission of human immunodeficiency type 1. *J Infect Dis.* 1997;175:1206–1210
 29. Manzini P, Saracco G, Cerchier A, et al. Human immunodeficiency virus infection as risk factor for mother-to-child hepatitis C virus transmission; persistence of anti-hepatitis C virus in children is associated with the anti-hepatitis C virus immunoblotting pattern. *Hepatology.* 1995;21:328–332
 30. Chang MH, Ni YH, Hwang LH, et al. Long-term clinical and virologic outcome of primary hepatitis C virus infection in children: a prospective study. *Pediatr Infect Dis J.* 1994;13:769–773
 31. Matsubara T, Sumazaki R, Takita H. Mother-to-infant transmission of hepatitis C virus: a prospective study. *Eur J Pediatr.* 1995;154:973–978
 32. Palomba E, Manzini P, Fiammengo P, Maderni P, Saracco G, Tovo PA. Natural history of perinatal hepatitis C virus infection. *Clin Infect Dis.* 1996;23:47–50
 33. Bortolotti F, Resti M, Giacchino R, et al. Hepatitis C virus infection and related liver disease in children of mothers with antibodies to the virus. *J Pediatr.* 1997;130:990–993
 34. Chang MH. Mother-to-infant transmission of hepatitis C virus. *Clin Invest Med.* 1996;19:368–372