Increased Risk of Maternal-Infant Hepatitis C Virus Transmission for Women Coinfected with Human Immunodeficiency Virus Type 1

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To estimate the risk of mother-to-child transmission of hepatitis C virus (HCV) and identify correlates of transmission, 245 perinatally exposed singleton children followed prospectively beyond 18 months of age were studied. Overall, 28 (11.4%) of the 245 children acquired HCV infection. Transmission occurred in 3 of 80 children (3.7%) whose mothers had HCV infection alone and in 25 of 165 (15.1%; P<.01) whose mothers had concurrent infection with human immunodeficiency virus type 1 (HIV-1). The percentage of HIV-1-infected children was similar (22 of 165, 13.3%), but each virus was transmitted independently; only six infants (3.6%) were coinfected with HCV and HIV-1. The risk of HCV transmission was not associated with maternal HIV-1-related symptoms, intravenous drug use, prematurity, low birth weight, or breast-feeding, whereas it was lower with cesarean section than with vaginal delivery (5.6% vs. 13.9%, P=.06). This suggests that transmission occurs mainly around the time of delivery.

Mother-to-child transmission of hepatitis C virus (HCV) is widely documented. However, in different investigations the estimated risk of infection ranged from zero to 100% [1–15]. This variability derives from differences in methods used to define the child’s infection status, duration of follow-up, and size and features of the populations studied.

Transmission of HCV may occur in utero via the transplacental route at any time during pregnancy, at the time of delivery, and postnatally through breast-feeding. Several factors might favor or hamper infection of the offspring. Identification of these factors would allow the adoption of rational preventive strategies and the offer of specific counseling, but little is known about the timing and correlates of transmission. High levels of viremia [5–7], certain HCV genotypes [8], and maternal coinfection with HIV-1 [1, 2, 4, 7, 9, 15] have been associated with increased HCV transmission rates, although the results are controversial [10–13]; breast milk does not seem to have a significant role [13–15].

The aim of this study was to quantify the rate of HCV infection in children born to mothers with or without HIV-1 coinfection. The effects of other possible correlates of transmission, such as maternal HIV-1 disease progression, history of intravenous drug use (IVDU), length of pregnancy, birth weight, mode of delivery, and type of feeding were also investigated.

Patients and Methods

Patients. A cohort of 245 children born to HCV-infected women were enrolled at 12 participating centers. In three centers all parturients were screened for HCV-seropositivity; in the remaining centers, HCV testing was mostly performed only for women who had a history of IVDU or were known to be HIV-1-infected. Only singleton at-risk infants identified within the first 2 weeks of life and followed up for at least 18 months were included in this study.

Data collection. Specific information was collected by questionnaire on maternal risk factors for HCV infection (IVDU, transfusions, sexual contact with an infected partner, other, unknown), mother’s HIV-1 infection status at delivery (presence or absence of specific antibody), length of pregnancy (weeks), mode of delivery (vaginal, elective/emergency cesarean), birth weight (grams), type of feeding (maternal, with duration of breast-feeding, or formula only), and age at first and last visit. The presence or absence of antibodies to HCV and HIV-1 as well as of HCV RNA (with dates of the tests) in the child was also reported.

Laboratory tests. Clinical examination and laboratory testing were performed every 3–5 months over the first 18 months of life; thereafter, only children with HCV and/or HIV-1 infection were regularly followed for a mean period of 28 months (range, 19–42 months), while most uninfected children were discharged or lost to follow-up. The mothers’ enrollment serum samples and follow-up samples from their children were tested for HCV-seropositivity by a second-generation EIA and a recombinant immunoblotting assay (RIBA II or RIBA III). Anti-
bodies to HIV-1 were measured by ELISA and confirmed by western blotting.

The presence of HCV RNA was investigated by reverse transcriptase PCR, performed by single participating centers. Total RNA was extracted from serum samples of perinatally exposed children; after a reverse transcription step, cDNA was amplified with commercial primers of the 5′ noncoding region of the viral genome in a single PCR of 35 cycles. PCR product was separated by agarose gel electrophoresis and visualized by ethidium bromide staining.

**Child’s HCV (and HIV-1) infection status.** Children were considered to be infected with HCV and/or HIV-1 when specific antibodies persisted beyond 18 months of age. Children with HCV RNA in at least two serum samples were also considered infected.

**Risk factors for transmission.** To assess the impact of maternal HIV-1 coinfection on transmission of HCV to the offspring, mother/child pairs were divided into two groups. Group A included 80 women with HCV alone, and group B included 165 women coinfected with HIV-1. The effects of other factors possibly related to HCV transmission were also evaluated. These included a history of IVDU, mother’s HIV-1 disease state, length of pregnancy, birth weight, mode of delivery, and type of feeding. The influence of the HIV-1-related maternal clinical condition was analyzed to enable grouping of women as asymptomatic or symptomatic at delivery; the latter included those with any HIV-1-associated symptoms or signs. The effects of prematurity and low birth weight were assessed to enable grouping of children according to gestational age and birth weight (< 36 weeks vs. ≥ 37 weeks and < 2,500 g vs. ≥ 2,500 g).

**Results**

In total, 28 of the 245 children (11.4%; 95% CI, 7.5–15.3) acquired HCV infection. Of 80 group A children, 3 (3.7%; 95% CI, 0.4–7.9) were HCV-seropositive after 18 months of age, while of 165 group B infants, 25 (15.1%; 95% CI, 9.6–20.6; P < .01) contracted HCV. In particular, 22 (13.3%) were seropositive before age 18 months. Of these 22, 20 (90.9%) had transaminase levels more than twice the normal values in several determinations. Another three HIV-1-uninfected children (1.8%) seroreverted but had HCV RNA detected in at least two separate determinations (one had 2 of 2 PCRs positive, one had 3 of 3, and the third had 2 of 7), with enhanced transaminase values in two cases. Consistent increases in transaminase levels were not observed among the remaining antibody-negative children.

PCR was performed for another 89 healthy seroreverting children (34 of group A and 55 of group B), with negative findings for all but two group B children, who had one inconsistently positive result and normal transaminase values (and were thus judged to be uninfected). HCV RNA was detected in 16 (84.2%) of 19 antibody-positive children. No substantial differences in HCV transmission were observed between the centers.

Of 165 group B children, 22 (13.3%) acquired HIV-1, including 6 (3.6%) coinfected with HCV.

Table 1 shows the influence of other possible risk factors on HCV transmission. The percentage of HCV-infected children was higher among those born by vaginal delivery than by cesarean section, with differences at the limit of significance in the cohort as a whole and in group B. No significant difference emerged in comparison of elective and emergency cesarean deliveries (2 of 50 [4%] vs. 2 of 21 [9.5%], respectively). Mode of delivery was also associated with transmission of HIV-1, with 20 (16.8%) of 119 HIV-1-infected children delivered vaginally and 2 of 46 (4.3%; P < .05) by cesarean section.

The presence of HIV-1-related symptoms in the mother was not predictive of HCV infection (table 1). Likewise, the proportion of children who acquired HIV-1 was comparable between asymptomatic and symptomatic mothers (12 of 76 [15.8%] vs. 10 of 78 [12.8%], respectively).

All infants born to HIV-1-positive women were bottle-fed. Thirty-three women with HCV infection alone breast-fed their babies, for a mean duration of 2.4 months (range, 0.5–12 months), with no increase in the HCV transmission rate (table 1).

A history of IVDU, prematurity, and low birth weight were not significantly associated with HCV transmission. These parameters did not influence HIV-1 infection either (data not shown).

**Discussion**

The results of this study highlight that vertical transmission of HCV is a rare event when the mother is uninfected with HIV-1; when she is also HIV-1-positive the risk of HCV infection of the infant increases significantly. High rates of HCV transmission in children whose mothers had concurrent HIV-1 infection have been reported [1, 2, 4, 7, 9, 15]. However, these investigations were based on small sample sizes. Furthermore, some included antibody-positive infants younger than 18 months of age as HCV-infected [7, 9, 15], and others had an unusually large proportion of healthy HCV carriers among seroreverting children [1, 2, 4].

The less-stringent criteria used in such studies to define HCV infection status may account for their substantially higher transmission rates in respect to that observed in the present analysis. Passively acquired maternal anti-HCV antibody usually becomes undetectable by 6–12 months of age, but it may persist longer in children born to mothers coinfected with HIV-1 [13]. In our setting, two group B children remained HCV-seropositive up to age 17 months and then seroreverted. Therefore, as established for HIV-1 [16], the diagnosis of HCV infection in perinatally exposed infants cannot be based on standard tests for IgG antibody to HCV before 18 months of age.
The presence of HCV RNA in some seroreverting children is an intriguing phenomenon. As in other recent investigations [5, 12, 13], we observed this phenomenon in few cases. PCR is a very sensitive technique to detect HCV RNA in serum samples from infected subjects, but the method has yet to be standardized, and false-positive results cannot be ruled out. To reduce this possibility, only children for whom results were positive in two separate determinations were considered to be HCV-infected.

On the other hand, not all seroreverters were tested by PCR, and its sensitivity was not absolute in antibody-positive children. In addition, results were not controlled in a central laboratory. With these limitations, the balance of evidence leads us to conclude that the proportion of seronegative HCV carriers among at-risk children is limited and thus should not bias the results of this study.

In areas where the HIV-1 epidemic has spread mostly because of IVDU, many women are coinfected with HCV. In Italy, about three-quarters of HIV-1-positive women are also HCV-positive [13, 15]. Whereas worldwide informational campaigns have been instituted for the prevention of mother-to-child HIV-1 transmission, the risk connected with HCV has not received adequate consideration. Our study points out that women faced with child-bearing decisions and pregnant women, particularly those with at-risk behaviors (e.g., IVDU), should be encouraged to undergo antenatal testing for both HIV-1 and HCV, and those with double infection should be informed about the additional risk of transmitting HCV to their offspring.

The greater HCV infectiousness of group B mothers may be accounted for by HIV-1-induced immunosuppression leading to impaired control of HCV, with consequent increased levels of viremia. A direct correlation has been found between maternal viral load and HCV transmission [5–7], although other investigators failed to find this association [13, 14].

The higher the degree of immunosuppression, viral burden, and disease progression in the mother, the greater the risk of vertical transmission of HIV-1 [17–22]. In the present analysis, HIV-1-related clinical manifestations were not predictive of HCV or HIV-1 transmission. This might be due to the relatively small number of mother/child pairs studied.

It is interesting that in women with HCV and HIV-1 coinfection, the transmission of the two viruses was similar. However, each virus was acquired independently, attesting to the fact that distinct mechanisms regulate their passage to the offspring. The fact that a substantial fraction of at-risk children escaping infection with HIV-1 are infected with HCV must be taken into due account, particularly because perinatal HCV infection can give rise to an indolent chronic infection with no clear signs of hepatitis [23].

Another common feature in transmission of HCV and HIV-1 was the lower percentage of infected children among those delivered by cesarean section. Increasing evidence supports the association between mode of delivery and perinatal

**Table 1. Influence of maternal and infant factors on transmission of hepatitis C virus (HCV).**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of infected children/total no. in category (%)</th>
<th>Entire cohort</th>
<th>Group A*</th>
<th>Group B²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>28/245 (11.4)</td>
<td>3/80 (3.7)³</td>
<td>25/165 (15.1)³</td>
<td></td>
</tr>
<tr>
<td>History of iv drug use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>24/186 (12.9)</td>
<td>0/34</td>
<td>24/152 (15.6)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>4/56 (7.2)</td>
<td>3/43 (7)</td>
<td>1/13 (7.7)</td>
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</tr>
<tr>
<td>Clinical progression of HIV-1 infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic mothers</td>
<td></td>
<td>13/78 (16.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic mothers</td>
<td></td>
<td>11/76 (14.5)</td>
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<tr>
<td>Gestational age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>£36 w</td>
<td>2/38 (5.3)</td>
<td>0/13</td>
<td>2/25 (8)</td>
<td></td>
</tr>
<tr>
<td>≥37 w</td>
<td>26/207 (12.6)</td>
<td>3/67 (4.5)</td>
<td>23/140 (16.4)</td>
<td></td>
</tr>
<tr>
<td>Birth weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;2,500 g</td>
<td>3/51 (5.9)</td>
<td>0/16</td>
<td>3/35 (8.6)</td>
<td></td>
</tr>
<tr>
<td>≥2,500 g</td>
<td>25/194 (12.9)</td>
<td>3/64 (4.7)</td>
<td>22/130 (16.9)</td>
<td></td>
</tr>
<tr>
<td>Mode of delivery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>24/172 (13.9)³</td>
<td>2/53 (3.8)</td>
<td>22/119 (18.5)³</td>
<td></td>
</tr>
<tr>
<td>Cesarean</td>
<td>4/71 (5.6)¹</td>
<td>1/25 (4)</td>
<td>3/46 (6.5)¹</td>
<td></td>
</tr>
<tr>
<td>Type of feeding</td>
<td></td>
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<tr>
<td>Breast-feeding</td>
<td></td>
<td>1/33 (3)</td>
<td></td>
<td></td>
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<tr>
<td>Formula-feeding</td>
<td></td>
<td>2/43 (4.6)</td>
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</tr>
</tbody>
</table>

NOTE. Inconsistencies in total number of children for each variable are due to incomplete data.

* Children of HCV-positive, HIV-1-negative mothers.

² Children of HCV-positive, HIV-1-positive mothers.

³ P < .01.

¹ P = .06.
HIV-1 infection [21, 22, 24]. For HCV, the difference was just above the threshold of significance in the present study, while a significant protective effect of cesarean section was observed by Paccagnini et al. [15].

Abdominal surgical delivery can protect infants from infection in several ways, as exposure to contaminated maternal blood during the passage through the birth canal is avoided as well as additional risks linked to episiotomy and instrumental delivery. Further protection may be derived from the prevention of maternal-fetal blood transfusions during labor.

The preventive action of cesarean section suggests that a large proportion of infants are infected around the time of delivery. In fact, when tested for in the first days of life, HCV RNA was undetectable in children who ultimately were shown to be infected in this and other investigations [5, 15, 23]. No difference in the HCV transmission rate was seen for children delivered by elective vs. emergency cesarean section. This could indicate that the infection occurs mainly during the passage through the birth canal, rather than at the onset of labor. If intrapartum transmission is responsible for the majority of perinatal HCV infections transmission then passive and/or active immunization of newborns may be a successful preventive intervention, analogous to hepatitis B virus.

Given the risk of HIV-1 transmission through breast-feeding, this feeding method was adopted only for group A infants, with no apparent increase in HCV infections. Other data support the view that postnatal HCV transmission via maternal lactation is unlikely [13–15]. Consequently, there is no evidence to discourage breast-feeding by women who are HCV carriers. Finally, it has been suggested that IVDU may facilitate the passage of HCV to the fetus and newborn [25], but IVDU was not associated with HCV transmission, nor was premature delivery or low birth weight.

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References