MAJOR ARTICLE

A Significant Sex—but Not Elective Cesarean Section—Effect on Mother-to-Child Transmission of Hepatitis C Virus Infection

European Paediatric Hepatitis C Virus Network[a]

(See the editorial commentary by Beasley and the article by Mast et al., on pages 1865–6 and 1880–9, respectively.)

Background. Risk factors for mother-to-child transmission of hepatitis C virus (HCV) are poorly quantified.
Methods. We conducted a European multicenter prospective study of HCV-infected pregnant women and their infants. Children with ⩾2 positive HCV RNA polymerase chain reaction test results and/or anti-HCV antibodies after 18 months of age were considered to be infected.

Results. The overall HCV vertical transmission rate was 6.2% (95% confidence interval [CI], 5.0%–7.5%; 91/1479). Girls were twice as likely to be infected as boys (adjusted odds ratio [OR], 2.07 [95% CI, 1.23–3.48]; $P = .006$). There was no protective effect of elective cesarean section (CS) delivery on HCV vertical transmission (adjusted OR, 1.46 [95% CI, 0.86–2.48]; $P = .16$). HCV/human immunodeficiency virus–coinfected women more frequently transmitted HCV than did women with HCV infection only, although the difference was not statistically significant (adjusted OR, 1.82 [95% CI, 0.94–3.52]; $P = .08$). Maternal history of injection drug use, prematurity, and breast-feeding were not significantly associated with transmission. Transmission occurred more frequently from viremic women, but it also occurred from a few nonviremic women.

Conclusions. Our results strongly suggest that women should neither be offered an elective CS nor be discouraged from breast-feeding on the basis of HCV infection alone. The sex association is an intriguing finding that probably reflects biological differences in susceptibility or response to infection.

An estimated 3% of the world's population is chronically infected with hepatitis C virus (HCV) [1]. The antenatal prevalence of infection in Europe ranges from <1% to 2.5% [2]. Estimates of the risk of mother-to-child (i.e., vertical) HCV transmission vary from 3% to 10% [3], but associations between risk and maternal and infant characteristics remain poorly quantified. Current knowledge on potential risk factors for vertical transmission is based on either retrospective analyses or studies of insufficient statistical power [3]. Research has focused on mode of delivery and infant feeding, since these are amenable to intervention. The debate on the protective role of elective cesarean section (CS) is open [4, 5], whereas most data agree that breast-feeding is not associated with the risk of transmission [2].

Maternal HCV load is likely to be the predominant risk factor for mother-to-child transmission of HCV. Although this has not been reliably quantified in large studies, it is supported by consistent findings of increased risk among HCV/HIV-coinfected women [4, 6, 7], who are thought to have higher HCV loads secondary to HIV-driven immunosuppression. However, HIV-infected women are now treated with potent antiretroviral therapy (ART), which strongly improves their immune response and reduces HIV transmission to offspring [8]; the question of whether this treatment also influences HCV transmission remains unanswered.

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Aiming to avoid the limitations of small sample sizes, the European Paediatric HCV Network (EPHN) was established in 1998 to form a large prospective, multicenter study to investigate issues related to mother-to-child transmission of HCV, including quantification of the effects of potential risk factors.

SUBJECTS AND METHODS

Subjects. HCV-infected pregnant women were enrolled at 33 EPHN centers; all diagnoses of HCV infection were made at or before delivery. Maternal, delivery, and infant information was recorded on specific registration and follow-up forms, which were sent to the London coordinating center. Data collected included the mother's likely mode of acquisition of HCV infection, maternal HIV coinfection and receipt of ART during pregnancy, maternal HCV viremia, mode of delivery, birth weight (in grams), gestational age (in completed weeks), and type of feeding (breast-feeding or formula). Children were followed in accordance with a standard protocol, with clinical examinations at birth; age 6 weeks; age 3, 6, 9, 12, 18, and 24 months; and thereafter every 6 months if infected or every year if uninfected. At each visit, blood was collected for laboratory tests, including qualitative polymerase chain reaction (PCR) for HCV RNA and anti-HCV antibody. Local ethics approval was obtained, and each woman gave consent before enrollment.

Children were considered to be infected if they had ⩾2 positive HCV RNA PCR test results and/or were anti-HCV antibody positive after 18 months of age (the age by which passively acquired maternal antibodies will have disappeared in all but very rare cases) [9]. Children were considered to be uninfected if they had <2 positive HCV RNA PCR test results and ⩾2 negative HCV RNA PCR test results and/or were anti-HCV antibody negative after 18 months of age. In addition, children who had no positive PCR test results and were antibody negative between ages 9 and 18 months were considered to be uninfected. The remaining children were considered to be of indeterminate infection status.

Second-born twins and second- and third-born triplets were excluded from the analysis. Elective CS deliveries were defined as those performed before the onset of labor and rupture of membranes (ROM). Prematurity was defined as <37 weeks gestation.

Statistical analysis. Data were entered into a Microsoft Access database, and statistical analyses were performed using STATA 8 (Stata Corporation). χ^2 tests were used to compare proportions. The Wilcoxon rank sum test was used to compare median maternal HCV loads by highly active ART (HAART) group and by infection status and to compare median duration of ROM by infection status, since the data were not normally distributed. Univariable and multivariable logistic regression was used to obtain odds ratio (OR) estimates for the effect of putative risk factors on the risk of vertical transmission. Because the HCV RNA PCR assays used to determine infection status vary between centers, and to allow for center-associated unobserved differences in background characteristics, we incorporated a random effect in the multivariable models at the center level.

RESULTS

Subject characteristics. By July 2004, 1787 mother-child pairs were enrolled at 33 EPHN centers in Italy, Spain, Germany, Ireland, the United Kingdom, Norway, and Sweden. There were 2 sets of triplets, 25 twin pairs, and a further 43 sibling pairs. All 6 children in the triplet sets were uninfected. Of the 25 twin pairs, 20 were concordant and uninfected, 1 was discordant (one infected, the other uninfected), 2 consisted of 1 uninfected twin and 1 indeterminate twin, and 2 consisted of 2 indeterminate twins. Of the 43 sibling pairs, 30 were concordant and uninfected, 3 were discordant, 5 had 1 infected sibling and 1 indeterminate sibling, 4 had 1 uninfected sibling and 1 indeterminate sibling, and 1 had 2 indeterminate siblings.

There were, thus, 1758 mother-child pairs (1731 singleton infants and 27 first-born infants from multiple pregnancies), of whom 279 children (16%) were of indeterminate infection status and 1479 (84%) had confirmed infection status. The latter group forms the basis of the analyses.

The 279 mothers of children of indeterminate infection status were similar to the 1479 mothers of children with confirmed infection status, except that they were significantly less likely to be HCV/HIV coinfected (7.2%; $P = .001$) and, therefore, were less likely to have had an elective CS (20%; $P < .001$). They were more likely to have a history of injection drug use (IDU) (58%; $P < .001$) and less likely to breast-feed (25%; $P = .03$).

Table 1 shows the characteristics of the 1479 women and children with confirmed infection status. Because elective CS is recommended for HIV-infected women to reduce the risk of HIV vertical transmission [10], the rate of elective CS was substantially higher in women with HCV/HIV coinfection (64%; 123/192) than in those with HCV infection alone (29%; 333/1139) ($P < .0001$). Within Europe, Italy is known to have a high rate of elective CS [11], and this was observed in the present study, with an overall elective CS rate in Italian centers of 38%; in non-Italian centers, this increased from 14.9% (54/363) before 2001 to 22.4% (30/134) since 2001 ($\chi^2 = 3.93$; $P = .05$).

The prematurity rate (<37 weeks) varied by maternal characteristics, from 12% (138/1111) among women with HCV infection only to 37% (72/197) among HCV/HIV-coinfected women. Among women who used injection drugs during pregnancy, 25% (28/112) had a premature delivery, as did 23% (54/237) of women with a history of IDU, compared with 10% (73/697) of those who had never injected drugs (history vs. no history of IDU, $P < .0001$). One-third of women breast-fed their

Table 1. Characteristics of 1479 hepatitis C virus (HCV)–infected women and their children.

Characteristic	Value
Maternal acquisition of HCV infection	
Blood transfusion/blood products	164 (12.1)
Injection drug use	447 (33.1)
Other	571 (42.3)
Not known	169 (12.5)
Missing	128
Maternal HIV infection status	
Infected	208 (15.0)
Uninfected	1183 (85.0)
Missing	88
Maternal injection drug use	
History	448 (38.6)
No history	714 (61.4)
Missing	317
Maternal age at delivery	
Mean (SD), years	31.7 (5.17)
Median (range), years	32.0 (17.1–45.1)
Missing	274
Mode of delivery	
Vaginal	764 (52.5)
Emergency CS	160 (11.0)
Elective CS	480 (33.0)
CS (unspecified)	51 (3.5)
Missing	24
Sex	
Male	802 (54.6)
Female	668 (45.4)
Missing	9
Gestational age	
Very premature (≤34 weeks)	97 (7.0)
Premature (35–36 weeks)	122 (8.8)
Term (≥37 weeks)	1163 (84.2)
Missing	97
Birth weight	
Low (<2500 g)	215 (15.8)
Normal (≥2500 g)	1142 (84.2)
Missing	122
Infant feeding type	
Breast-fed	452 (32.7)
Formula fed	930 (67.3)
Missing	97
Child HIV infection status	
Infected	10 (0.7)
Uninfected	1397 (97.4)
Indeterminate	28 (1.9)
Missing	44

NOTE. Data are no. (%) of subjects, unless otherwise specified. CS, cesarean section.

infants overall—38% (428) of those with HCV infection only and just 1.5% (3) of those with HCV/HIV coinfection.

Risk of and risk factors for vertical transmission. The overall HCV vertical transmission rate was 6.2% (95% confidence interval [CI], 5.0%–7.5%; 91/1479). The HCV transmission rate was higher from HIV-coinfected women (8.7%; 18/208) than from women with HCV infection only (5.5%; 65/1183), although this difference was not statistically significant (unadjusted OR, 1.63 [95% CI, 0.94–2.81]; $P = .08$). Maternal history of IDU was not associated with risk of transmission: 6.3% (28/448) of babies born to women with any history of IDU were infected, compared with 6.2% (44/714) of babies born to women with no history of IDU (unadjusted OR, 1.02 [95% CI, 0.62–1.66]; $P = .95$). Similarly, there was no difference in transmission risk between women who used injection drugs during pregnancy and those who had a history of IDU but did not use injection drugs during pregnancy (7.1% [8/113] vs. 7.0% [17/244]; $\chi^2 = 0.0015$; $P = .969$). The transmission rate did not vary significantly by mode of delivery (elective CS, 7.3% [35/480]; vaginal delivery or emergency CS, 5.4% [50/924]; unadjusted OR, 1.37 [95% CI, 0.88–2.15]; $P = .16$). Girls were twice as likely to be HCV infected as boys (girls, 8.2% [55/668]; boys, 4.2% [34/802]; unadjusted OR, 2.03 [95% CI, 1.30–3.15]; $P = .001$). Of premature babies, 4.1% (9/219) were HCV infected, compared with 6.3% (73/1163) of those born at 37 weeks or later (unadjusted OR, 0.64 [95% CI, 0.32–1.30]; $P = .21$). The proportion of infected children was similar in the breast-fed (4.9%; 22/452) and formula fed (5.7%; 53/930) groups (unadjusted OR, 0.85 [95% CI, 0.51–1.41]; $P = .52$).

Table 2 shows the results of univariable and multivariable analyses of the 1220 mother-child pairs with information available on all variables. The univariable ORs for the subset of 1220 children were generally similar to those obtained using all available data for each variable, as above, and showed significant associations between vertical transmission risk and maternal HIV coinfection, mode of delivery (borderline), and sex. In multivariable analysis, sex remained the only risk factor significantly associated with HCV vertical transmission. The multivariable analysis was repeated, adjusting for maternal history of IDU, since this was reported to be associated with a higher HCV transmission rate elsewhere [12]. Here, maternal history of IDU was not associated with transmission (unadjusted OR, 0.99 [95% CI, 0.59–1.67], $P = .97$; adjusted OR, 1.33 [95% CI, 0.71–2.50], $P = .38$), and the estimated ORs for the other variables were not altered substantially, although the adjusted OR for maternal HIV coinfection increased to 2.18 and became statistically significant (95% CI, 1.02–4.65; $P = .04$).

Maternal HCV/HIV coinfection. Of the 208 HCV/HIV-coinfected women, 6.2% (10) had an HIV-infected child, 1 of whom was also HCV infected (HIV infection status was indeterminate for 27 and was missing for 20). Of these 10 women, 2 received HAART during pregnancy, 6 received other ART, and 2 were untreated. All except 1 child received ART neonatally. Women with HCV/HIV coinfection differed from those with HCV infection only for several of the factors of interest, in light of recommendations to prevent mother-to-child HIV

Table 2. Risk of transmission and associated maternal and infant characteristics for 1220 children (65 HCV infected and 1155 HCV uninfected) with information available on all variables.

	Unadjusted		Adjusted for all other variables	
Characteristic	OR (95% CI)	*P*	OR (95% CI)	*P*
Maternal HIV infection status				
Uninfected	1.0		1.0	
Infected	1.89 (1.05–3.40)	.03	1.82 (0.94–3.52)	.08
Mode of delivery				
Vaginal or emergency CS	1.0		1.0	
Elective CS	1.66 (1.00–2.74)	.05	1.46 (0.86–2.48)	.16
Sex				
Male	1.0		1.0	
Female	2.12 (1.27–3.56)	.004	2.07 (1.23–3.48)	.006
Prematurity				
Term	1.0		1.0	
Premature	0.54 (0.23–1.26)	.15	0.45 (0.19–1.08)	.07
Infant feeding type				
Formula fed	1.0		1.0	
Breast-fed	0.74 (0.42–1.31)	.30	0.88 (0.48–1.61)	.68

NOTE. CI, confidence interval; CS, cesarean section; OR, odds ratio.

transmission [10]. For example, the former group more frequently had an elective CS (64% [123] vs. 29% [333]) and a premature delivery (37% [72] vs. 12% [138]), and only 1.5% (3) breast-fed, compared with 38% (428) of the latter group. To investigate whether the association between vertical transmission and maternal and infant factors differed in these 2 groups, we repeated the regression analyses, stratifying by maternal HIV coinfection (table 3). Mode of delivery was not associated with risk of transmission in either group. In both groups, girls were significantly more likely to be infected than boys. Among the HCV/HIV-coinfected women, prematurity was associated with a significantly lower HCV transmission rate, although in multivariable analysis this difference was no longer statistically significant. Breast-feeding was not statistically significantly associated with transmission in women with HCV infection only, although its effect could not be estimated in the coinfected women, since only 3 breast-fed and their children were all uninfected.

HAART is now widespread among HIV-infected pregnant women. Of 184 HCV/HIV-coinfected mothers, 81 received HAART during pregnancy, 71 received monotherapy, and 32 were not treated. HAART was associated with a substantial but only marginally significant reduction in the risk of HCV transmission (table 3). Its use has been shown to increase the risk of prematurity [13], and women who received HAART delivered prematurely more frequently than did those who received monotherapy or no therapy (36/81 [44%] and 29/103 [28%], respectively; $\chi^2 = 5.27$; $P = .02$). Because HAART reduces HIV load and improves the associated immunosuppression, it might also affect HCV load and, thereby, vertical transmission of HCV. There was a trend toward lower HCV load among HAART-treated women, compared with women receiving monotherapy or no therapy; the median HCV load among 18 HAART-treated women was 656,101 copies/mL, versus 850,000 copies/mL among 11 women receiving monotherapy or no therapy ($z = -0.922$; $P = .36$).

Maternal HCV viremia. Of the women whose children had confirmed HCV infection status, 556 had at least 1 qualitative and/or quantitative PCR test result for HCV RNA during pregnancy, at delivery, or in the first week postpartum (median, 1 test [range, 1–5 tests]). Of these, 394 (70.9%) were viremic, 153 (27.5%) were nonviremic, and 9 (1.6%) had both positive and negative PCR test results.

Being tested for viremia was not associated with particular centers or with possible risk factors for vertical transmission (the variables in table 2). Women with HCV/HIV coinfection were significantly more likely to be viremic than were those with HCV infection only (91% vs. 69%; $\chi^2 = 16.60$; $P < .001$), and breast-feeding was less frequent among viremic women than among nonviremic women (27% vs. 43%; $\chi^2 = 13.19$; $P < .001$).

Of the 403 women who were ever viremic, 6.2% (25) had an HCV-infected child, compared with 3.3% (5) of the 153 women who were never viremic (unadjusted OR, 1.96 [95% CI, 0.73–5.22]; $P = .17$). Adjusting for sex, maternal HIV coinfection, mode of delivery, breast-feeding, and prematurity, either individually or simultaneously, did not alter the OR estimate (fully adjusted OR, 1.96 [95% CI, 0.71–5.40]; $P = .19$). The limited sample size and small number of transmission events may explain the nonsignificant result.

Only 221 of the 403 women who were ever viremic had at

Table 3. Associations between maternal and infant characteristics and vertical transmission, stratified by maternal HIV infection status

Maternal infection status, characteristic	Unadjusted		Adjusted[a]	
	OR (95% CI)	*P*	OR (95% CI)	*P*
HCV/HIV coinfected (n = 184)				
Mode of delivery				
Vaginal or emergency CS	1.0		1.0	
Elective CS	1.20 (0.40–3.62)	.75	0.76 (0.23–2.53)	.66
Sex				
Male	1.0		1.0	
Female	3.80 (1.18–12.26)	.03	4.00 (1.18–13.54)	.03
Prematurity				
Term	1.0		1.0	
Premature	0.11 (0.01–0.83)	.03	0.14 (0.02–1.13)	.07
Maternal ART				
Monotherapy/none	1.0		1.0	
HAART	0.27 (0.07–0.97)	.05	0.26 (0.07–1.01)	.05
HCV infected only (n = 1034)				
Mode of delivery				
Vaginal and emergency CS	1.0		1.0	
Elective CS	1.57 (0.88–2.83)	.13	1.59 (0.88–2.86)	.13
Sex				
Male	1.0		1.0	
Female	1.79 (1.00–3.22)	.05	1.80 (1.00–3.24)	.05
Prematurity				
Term	1.0		1.0	
Premature	0.83 (0.32–2.13)	.69	0.83 (0.32–2.15)	.70
Infant feeding type				
Formula fed	1.0		1.0	
Breast-fed	0.88 (0.48–1.61)	.68	0.92 (0.50–1.70)	.80

NOTE. An odds ratio (OR) could not be calculated for the effect of infant feeding among the coinfected group, because only 3 women breast-fed and all of their children were uninfected. The infant feeding variable was therefore excluded from the multivariable model. ART, antiretroviral therapy; CI, confidence interval; CS, cesarean section; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus.

[a] Adjusted for sex, prematurity, mode of delivery, and HAART for the coinfected group; adjusted for sex, prematurity, mode of delivery, and infant feeding type in the group infected with HCV only.

least 1 quantitative PCR test result. The median HCV load was 412,500 copies/mL (range, 30–48,210,000 copies/mL) and was higher among the mothers of 16 infected children (475,000 copies/mL [range, 15,400–13,406,441 copies/mL] vs. 409,000 copies/mL [range, 30–40,550,000 copies/mL]; $z = -0.84$; $P = .40$). Further investigation of the association between HCV load and transmission risk was not possible with only 16 infected children.

ROM. The time from ROM to delivery (i.e., the duration of ROM) was reported for 466 women whose children had confirmed infection status and were delivered vaginally (400) or via emergency CS (62) (CS type was unspecified for 2 and missing for 2). Among the 19 women with an infected child, the median duration of ROM was 4.5 h (range, 10 min–27.25 h), compared with 2.6 h (range, 1 min–90 h) among the 447 women with an uninfected child ($z = -2.130$; $P = .03$). For each 1-h increase in duration of ROM, the risk of vertical transmission increased by ~3% (unadjusted OR, 1.03 [95% CI, 0.99–1.06]; $P = .11$).

Sensitivity analyses. Twenty-five infected children had evidence of viral clearance and became antibody negative after 18 months; in some cases, although qualitative PCR test results were positive on ⩾2 occasions, viremia was undetectable by quantitative PCR at these times. We therefore repeated the main analysis reported in table 2, excluding these 25 infected children. The overall transmission rate decreased from 6.2% to 4.5% (66/1454 [95% CI, 3.5%–5.7%]), but the results concerning correlates of transmission did not change substantially, except that the OR estimates for maternal HCV/HIV coinfection increased substantially and became statistically significant (adjusted OR, 4.48 [95% CI, 2.10–9.58]; $P < .001$). Maternal history of IDU was associated with transmission in univariable (unadjusted OR, 1.80 [95% CI, 1.01–3.21]; $P = .04$) but not multivariable (adjusted OR, 0.91 [95% CI, 0.43–1.92]; $P = .80$) analysis. In stratified analysis, results for the HCV/HIV-coinfected women remained as reported in table 3, because none of the 25 excluded children were born to coinfected women. Among the women with HCV infection only, the ad-

justed OR estimate for sex increased a little, to 2.34 (95% CI, 1.03–5.30; $P = .04$). Repeating the analyses with the 25 children included as uninfected (rather than excluding them from the analysis) gave very similar results.

The analyses were also repeated including only children with infection status confirmed by antibody status at or after 18 months of age. Results were similar to those of the main analysis shown in table 2, except that the adjusted OR estimate for maternal HIV coinfection increased to 3.95 (95% CI, 1.19–13.08; $P = .03$) and the estimate for sex increased to 6.42 (95% CI, 1.40–29.35; $P = .02$).

Allowing for potential center differences. Incorporating a random effect in the multivariable models at the center level improved the goodness of fit of the models for all women and for the subgroup with HCV infection only but not for the HCV/HIV-coinfected women. However, in all cases, the association between transmission risk and the risk factors did not change, and the OR estimates and *P* values were similar.

DISCUSSION

HCV infection is a major public health problem and is of particular concern during pregnancy. Identification of transmission risk factors is essential for the development of appropriate interventions. In this large, prospective European cohort, girls were twice as likely to be infected as boys. There was no evidence of a protective effect of elective CS delivery. However, the duration of ROM was significantly longer among mothers of infected children than among mothers of uninfected children. HCV/HIV-coinfected women were more likely to transmit HCV to their infants than were women with HCV infection only, although this was not statistically significant in multivariable analysis. An increased but not statistically significant risk of transmission was also observed among women who were HCV viremic during pregnancy or around the time of delivery, although a few children were infected by nonviremic women. Maternal history of IDU, prematurity, and type of infant feeding were not significantly associated with transmission.

To our knowledge, this is the first report of a significant association between sex and HCV vertical transmission. Granovsky et al. reported an 8% transmission risk for girls, compared with 3% for boys, in a study of 122 mother-child pairs with 7 infected children, but this difference was not statistically significant [14]. A significantly higher susceptibility of females to vertically acquired infections has been observed for human T cell leukemia/lymphoma virus type I [15] and for HIV in Europe [16] and in Malawi [17], although the risk of postnatal HIV transmission was found to be significantly higher in males in a meta-analysis of African trials [18]. Because the male:female ratio in our study population was higher than that observed in the general population, this finding is unlikely to be due to excessive deaths of infected males in utero. It likely reflects hormonal or genetic differences in susceptibility or response to infection between males and females. Maternal infections increase fetal cortisol and dehydroepiandrosterone synthesis [19]. Androgens may influence the immune response [20]; estradiol protects stimulated feline lymphocytes from apoptosis [21], and human male and female fetuses exhibit differences in regulation of the cytokine network [22]. Sex differences in mortality associated with routine childhood modified virus vaccinations may also indicate differential susceptibility to infection [23].

Until recently, maternal HCV/HIV coinfection was consistently found to be associated with an increased risk of HCV vertical transmission [4, 6, 7], thought to be mediated by the higher HCV load in immunosuppressed HCV/HIV-coinfected women than in women with HCV infection only. The attenuation of this association seen in the present study is likely to be due to the recent widespread use of HAART, which substantially improves HIV-induced immunosuppression and, consequently, may lead to better control of HCV replication; a similar finding was reported in a small study involving 15 HCV/HIV-coinfected ART-treated women [24]. Our results suggest that HAART may reduce both maternal HCV load and risk of HCV transmission. Since HAART causes prematurity [13], it can also account for the apparent protective effect of prematurity on HCV vertical transmission, seen only in HCV/HIV-coinfected women.

Although the risk of vertical transmission is likely to be substantially lower in nonviremic women, our results confirm our previous finding [9] that it cannot be ruled out, since a few children acquired infection from nonviremic women. Data on maternal HCV viremia must be interpreted with caution, since fluctuations may occur during pregnancy [25]. The results of 1 or 2 PCR tests during pregnancy or at delivery do not necessarily reflect viremia status at the relevant time for transmission. Viral load may be a better predictor of transmission than a qualitative test. However, even where viral load data are available, interpretation is problematic, especially in multicenter studies, because of interlaboratory and interassay variations [26].

The proportion of elective CS was high in our study among HCV/HIV-coinfected women, for whom a targeted recommendation exists [10], as well as among those with HCV infection only, especially in Italian centers, where this practice is common among the general population [11]. Our current findings make an important contribution to the debate [4, 5, 24, 27–29] and strongly suggest that mode of delivery does not influence HCV transmission in women with HCV infection only or in HCV/HIV-coinfected women when they are receiving potent ART. This study would have been large enough to detect a 60% reduction in risk of transmission associated with elective CS delivery, from 6% to 2.5% (with 80% power and 5% significance). Consistent with the findings of Spencer et al. [30], it is of note that, despite the lack of a protective effect of elective CS, the

duration of ROM was related to transmission risk. Finally, our results confirm [6, 12, 30, 31] that breast-feeding does not increase the risk of HCV transmission, and, unlike Resti et al. [12], we did not observe an association between history of maternal IDU and HCV vertical transmission.

In observational studies, there is always a concern that unobserved factors may exist that could be related to the outcome of interest. However, although the goodness of fit of our models improved after the inclusion of a random effect in multivariable models—suggesting that there may be small center-associated differences in vertical transmission risk—the estimated associations between the variables of interest here and the risk of HCV vertical transmission did not change.

What are the implications of our findings for the clinical management of HCV-infected women? The overall risk of vertical transmission is low for women with HCV infection only but cannot be ruled out even in nonviremic mothers. Given that there is no antiviral treatment available for use during pregnancy, there are currently no interventions to prevent mother-to-child HCV transmission. In particular, there is no evidence to suggest that women should be offered an elective CS delivery or be advised to avoid breast-feeding. HCV/HIV-coinfected women are currently treated with HAART during pregnancy to prevent HIV vertical transmission; this treatment may also have a beneficial effect on HCV vertical transmission.

EUROPEAN PAEDIATRIC HEPATITIS C VIRUS NETWORK COLLABORATORS

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