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MAJOR ARTICLE

Single Clinical Practice's Report of Testing Initiation, Antibody Clearance, and Transmission of Hepatitis C Virus (HCV) in Infants of Chronically HCV-Infected Mothers

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Background. Perinatally acquired hepatitis C virus (HCV) is the main source of pediatric HCV infection. However, the best time for initiation of screening and follow up of these infants is still unknown. Analysis of the clinical data of infants born to HCV-infected mothers, transmission rates, and pathway of HCV testing could be important for optimization of their management.

Methods. Children of mothers with chronic HCV infection, who were observed between 1998 and 2013 at the pediatric infectious disease clinic for the first 18 months of their life, were eligible for enrollment. We analyzed the factors influencing initiation of HCV testing in these children and rate of HCV transmission as demonstrated by consecutive HCV antibody and HCV ribonucleic acid (RNA) amplification testing.

Results. One hundred and forty-two mother-infant pairs were enrolled. The majority of mothers were intravenous drug users, had carried to term, and delivered vaginally. A high proportion of infants had at least 1 positive anti-HCV antibody assay without viremia. True HCV infection and intermittent viremia were recorded in 3.5% and 1.4% of infants, respectively. Initiation of HCV testing after 10 months of age was associated with a significant decline in the probability of obtaining a positive HCV antibody of maternal origin.

Conclusions. The low likelihood for detection and confirmation of true HCV transmission before 10 months of age could challenge the early initiation of HCV screening of infants exposed to maternal HCV infection but may affect the parental need for early monitoring and counseling.

Keywords. diagnosis; HCV; pediatrics; perinatal transmission.

Hepatitis C virus (HCV) infection is classified as the leading cause of acquired chronic liver disease in children attributable to vertical mother-to-infant transmission [1–3]. The World Health Organization has identified children as a population at increased risk for HCV infection [4] due to seroprevalence of HCV in approximately 2.5% of pregnant women, with detectable hepatitis C viremia in 60% of cases [5]. The level of maternal HCV viremia, prolonged rupture of membranes, use of invasive fetal monitoring, and coinfection with human immunodeficiency virus (HIV) have been recognized as risk factors for vertical transmission of HCV [6, 7]. Although the extent of mother-to-infants HCV transmission is still not clear [6, 8], concern regarding HCV infection in children has emerged in recent years [2, 9]. Approximately 3% of the children infected with HCV show significant liver pathology [10]. In this regard, infants born to intravenous drug using mothers with HCV infection are at the greatest risk for persistent viral replication and the development of end-stage liver disease [11]. Treatment of infected children is being considered [7] despite the absence of approved medications [12].

Lack of clear evidence for any of the strategies to reduce vertical HCV transmission [13] and absence of an effective HCV vaccine [14, 15] demonstrate the need for timely diagnosis of HCV infection in children. The American Academy of Pediatrics recommends anti-HCV antibody testing after 12 months of age in infants born to mothers with HCV infection and without routine testing for HCV ribonucleic acid (RNA) [16]. The National Institutes of Health suggests initially testing for HCV RNA between the age of 2 and 6 months and later for anti-HCV after the infant is 15 months old [12]. The European Society and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition endorses testing for HCV antibodies when the infant is 18 months old [2]. The Centers for Diseases Control and Prevention advises initiation of HCV testing before 18 months, which

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includes testing for HCV RNA after 1 to 2 months of age with further detection of HCV viremia, irrespective of the initial results [17].

The present study was designed to describe the management patterns of infants born to mothers with chronic HCV infection being followed at a single clinical setting, the rate of HCV transmission, and HCV testing results with respect to the infant's age at HCV testing initiation, and their follow up. Analysis of HCV-related practices could be important for the optimization of management strategies for infants exposed to maternal HCV infection.

METHODS

The study was approved by the Jersey Shore University Medical Center Institutional Review Board. A cohort of infants born between 1998 and 2013 (inclusive) to mothers with chronic HCV infection and observed during the first 18 to 24 months of age at the Pediatric Infectious Disease Clinic were included in this study if the results of the anti-HCV and HCV-RNA testing were available for review in medical records. We collected demographic and clinical data, including the route of HCV transmission to mother (intravenous drug use, sexual contacts, and "other"), stage of maternal HCV disease (acute or chronic), mode of delivery, infant's gestational age at birth, type of feeding, and the results of consecutively tested anti-HCV antibody and HCV RNA in the infant's blood with time points (postpartum age).

Methods of Anti-Hepatitis C Virus (HCV) and HCV-Ribonucleic Acid Test Results

Results of the serological tests for HCV antibody and nucleic acid amplification tests for HCV RNA were obtained from the medical records. The HCV antibodies were tested in clinical laboratories that used US Food and Drug Administration-approved immunoassays and the qualitative HCV-RNA reverse transcriptase-polymerase chain reaction (PCR). The qualitative results (positive or negative) for HCV antibodies and HCV RNA were reported uniformly for all subjects and hence were used in this study for comparison of test results.

Assessment of Anti-Hepatitis C Virus (HCV) Antibodies and HCV-Ribonucleic Acid Test Results

We defined "HCV infection" if the infant had at least 2 positive HCV-RNA test results and positive HCV antibodies at or after 18 months of age [18, 19]. Infants who were initially PCR positive for HCV RNA but subsequently negative for HCV RNA and negative for HCV antibodies after 12 months of age were described as having "intermittent viremia or accelerated natural clearance of HCV infection" [20]. "Absence of HCV infection" was defined if the infant was negative for HCV RNA and anti-HCV antibodies between 9 and 15 months of age [19]. Infants with positive anti-HCV antibody followed by negative antibody test results and negative HCV RNA during the observation period were described as having "spontaneous clearance of anti-HCV maternal antibody" [21, 22].

Data Analysis

Incidence of vertical transmission of HCV was calculated by dividing the number of the HCV infection diagnosed infants by the total number of infants that were perinatally exposed to HCV infection. The results of initial testing for HCV antibodies and HCV RNA were assessed using χ^2 test for comparison with respect to the infant's age (months) at which samples were obtained. We used multiple regression models to analyze the link between the number of tests performed for HCV antibodies and HCV RNA during the first 18 months with the infant's age at which initial HCV testing was performed. Results (positive or negative) of the initial HCV testing (anti-HCV and HCV RNA) were included in the models. Correlation analysis was used to identify the relationship between the infant's year of birth and age at initiation of anti-HCV antibody testing. We used multiple regression analysis to identify the factors associated with the infant's age at detection of clearance of maternal HCV antibody. Data are presented as mean ± standard deviation, percentage, and 95% confidence interval (CI) of proportion, regression coefficient ± standard error, and correlation coefficient (r). STATISTICA 12.0 was used to perform the analysis. *P* value <.5 was used to define statistical significance.

RESULTS

Of the 144 infants born to mothers with chronic HCV infection, 142 infants were included in the final analysis. Two mother-infant pairs were excluded because of missing HCV-RNA results. Of the studied mother-infant pairs, 93.7% mothers were intravenous drug users (IVDUs), 2.1% were HIV positive, and 77.5% had delivered vaginally. Gestational age equal to or more than 35 weeks and formula feeding were recorded in 96.5% and 90.8% of the infants, respectively. Among the 142 infants observed over the first 18 months of their life, 3.5% were diagnosed with HCV infection, 1.4% had intermittent viremia, 66.9% had at least 1 positive result of anti-HCV antibody and negative HCV RNA, and 28.2% had negative anti-HCV antibody and HCV RNA.

Narrative of Hepatitis C Virus-Infected Infants

As shown in Table 1, infants diagnosed with HCV infection were born vaginally to IVDU mothers and were on formula feedings. One mother was coinfected with HIV. The infant's age at which HCV testing was initiated and the number of tests conducted over the first 18 months of life were unpredictable. Seroconversion and positive viremia were confirmed after 18 months of age in all patients including those with normal aminotransferase levels. All infants diagnosed with HCV were referred to the pediatric gastroenterologist/hepatologist for follow up.

Narrative of Cases With Single Positive Hepatitis C Virus-Ribonucleic Acid Test

Two infants that tested positive once with HCV RNA (at 4 and 6 months) had negative PCR test results for HCV RNA at 5 and

Table 1. Description of Infants Diagnosed With HCV Infection

	Characteristics of Clinical Data				Time Point (Age, Month) of the HCV Testing			
					Initial		Follow up	
Cases/Year	GA (Weeks)	MOD	Feeding	HIV	Anti-HCV	HCV RNA	Anti-HCV	HCV RNA
1999	36	Vaginal	Formula	–	1	1	2, 6, 12, 17, 18, 21	2, 6, 12, 17, 18, 21
2006	37	Vaginal	Formula	–	18	18	21	21
2006	38	Vaginal	Formula	+	2	2	3, 4, 6, 12, 18, 21	3, 4, 6, 12, 18, 21
2007	36	Vaginal	Formula	–	18	18	21	21
2008	40	Vaginal	Unknown	–	14	14	18, 21	18, 21

Abbreviations: GA, gestational age; HIV, hepatitis C virus; MOD, mode of delivery.

14 months in 1 infant and at 8, 9, and 14 months in the second child. All had negative anti-HCV antibodies at 14 and 15 months of age, respectively. Negative results for HCV RNA, HCV antibody, and transaminase after 18 months supported the evidence for spontaneous clearance of HCV infection.

Time of Hepatitis C Virus Antibodies Clearance

Among the 137 noninfected infants, follow-up testing in the clinic revealed negative HCV antibodies in 44 (32.1%) infants, including 27 that had tested negative for HCV antibodies once between 12 to 18 months of age, and 17 infants that had tested negative for HCV antibodies during follow up at 2 to 16 months of age. Ninety-three infants with initial positive HCV antibody were retested once (1.1%), 2 times (54.8%), 3 times (35.5%), and 4 or 5 times (8.6%). Clearance of HCV antibody was recorded in 27.4% of the infants before 12 months and 48.5% at 12 to 16 months; on average at the age of 14.0 ± 2.7 months. Age at HCV antibody clearance was indirectly associated with the number of tests performed ($b = -0.393 \pm 0.099$, $P < .002$) and independent of the age at which HCV antibody testing was initiated.

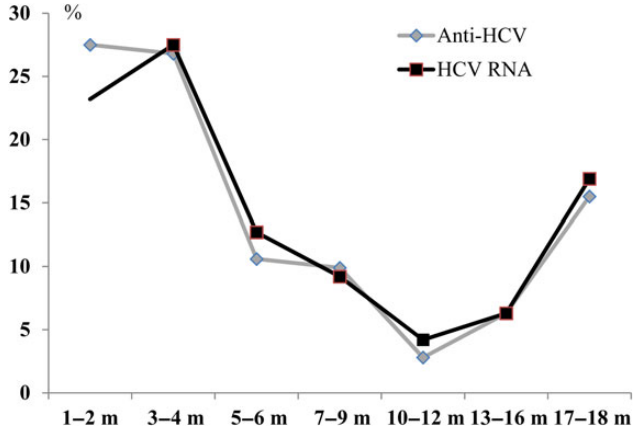

Figure 1. Age of infants when testing of anti-hepatitis C virus (HCV) antibodies and HCV RNA were initiated.

Hepatitis C Virus Testing Time Initiation and Results

In approximately 50% of infants, testing for HCV antibody and RNA was initiated during the first 4 months of life (Figure 1). Age at initiation of HCV antibody and HCV-RNA testing correlated with the infant's year of birth ($r = 0.27$, $P < .002$ and $r = 0.30$, $P < .01$). The number of infants that were tested initially at age 10 to 12 months decreased to approximately 5% and then increased to 16% at age 17 to 18 months (Figure 1). Negative HCV antibody at first testing was recorded in 13.2% (95% CI, 6.8%–19.6%) of infants at 1 to 9 months of age and in 84.8% (95% CI, 65.0%–104.2%) of infants at 10 to 16 months of age ($P < .001$). Irrespective of the time of testing initiation, only a few initial HCV-RNA tests were positive throughout the 18 months.

DISCUSSION

The likelihood for occurrence of nearly 7000 prenatally acquired new cases of pediatric HCV infection is a subject of public health concern due to the high healthcare expenditure associated primarily with the need for screening and monitoring of HCV status in infants exposed to maternal HCV infection [2, 3, 23, 24]. The lack of clear evidence regarding best practices is the main reason for the inconsistency in the existing recommendations regarding the time of initiation and subsequent testing for HCV in infants born to mothers with chronic HCV infection. To a certain extent, the observational data reflects the management of infants exposed to maternal HCV infection and therefore allows the analysis of the HCV transmission rate and HCV testing pathway. The HCV transmission rate of 3.5% that we identified was comparable to the 4%–7% rate reported in infants born to mothers with HCV and without HIV infection [1, 5, 24–26]. Similar to the 59 cases reported in the review by Yeung et al [27], a few infants in our study were classified as having intermittent viremia or clearance of mother-to-infant–acquired HCV infection. The finding of 2 cases with intermittent viremia among the 4 infants who tested positive at age 6 months or less was consistent with the results of a prospective study from Egypt [28]. It supports the incomplete predictability of the HCV-RNA test results obtained during

infancy despite the 70%–85% sensitivity of HCV-RNA testing after the first month of age and 98% specificity regardless of the age at which the HCV RNA was evaluated [19]. Our data show that detection of HCV antibody clearance at a younger age for the infant was associated with the performance of an increased number of tests. We also found that variation in the time of HCV screening initiation was associated with the infant's birth year, reflecting the variability in the publications over the years [2, 12, 16, 17]. Initiation of HCV antibody testing at an age between 10 and 16 months was associated with a significant decline in the probability of obtaining positive anti-HCV test results, which supports the limited value of early testing for HCV antibodies in infants exposed to maternal HCV infection [29, 30]. It has been shown that the probability for detection of HCV infection in children after 36 months is 5 times higher compared with that at 18–23 months [26].

There are several limitations of the present report. We recognize the limitation of the unstandardized time frame that was used for the HCV testing, even though the infant's ages at HCV testing initiation and HCV antibody clearance were analyzed with respect to the year of birth, age of HCV testing initiation, and number of tests performed. The generalizability of our results remains questionable, despite using population-based data and including a substantial number of observed infants. However, analysis of data from clinical practices is important for understanding the delivery of medical care, assessment of performance, and making suggestions regarding the improvement of management to the target population. Even though we used retrospectively collected clinical information, it allowed the estimation of the risk for mother-infant HCV transmission and understanding of the variability in HCV screening initiation and anti-HCV antibody clearance. It is obvious that in a retrospective study, the availability of information is restricted by the inclusion of measured variables, and therefore unmeasured variables may confound the results. For instance, we were not able to obtain maternal HCV-RNA genotype and levels that may correlate with the risk of mother-infant HCV transmission [31]. The infants in our study were born to a homogenous population of chronically HCV-infected drug users, which placed them at increased risk for vertical transmission [11, 32]. Although there is no compelling evidence that risk for vertical transmission is associated with HCV genotype, approximately 70% of IVDUs could be classified as having genotype 3a [33, 34]. Moreover, it is possible that during the time frame of the study, the sensitivity of the HCV-PCR testing might have changed. However, the lower limit for detection of HCV RNA of 50 IU/mL did not change, and the estimated specificity of the qualitative tests used during the study period was approximately 99.5% [35].

CONCLUSIONS

Due to the high probability for detection and clearance of maternal HCV antibody during infancy and cases of intermittent viremia, postponement of the initiation of anti-HCV antibody and RNA testing for up to 18 months is a reasonable approach in the management of infants born to mothers with chronic HCV infection. However, we concur with previous suggestions [20] that detection of HCV viremia at an early stage is important for the families who want to know about their infant's HCV status in order to receive proper counseling and continuity of medical management as well as consideration for treatment.

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