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Early Postnatal Polymerase Chain Reaction Testing in the Identification of Perinatal Transmission of Hepatitis C Virus

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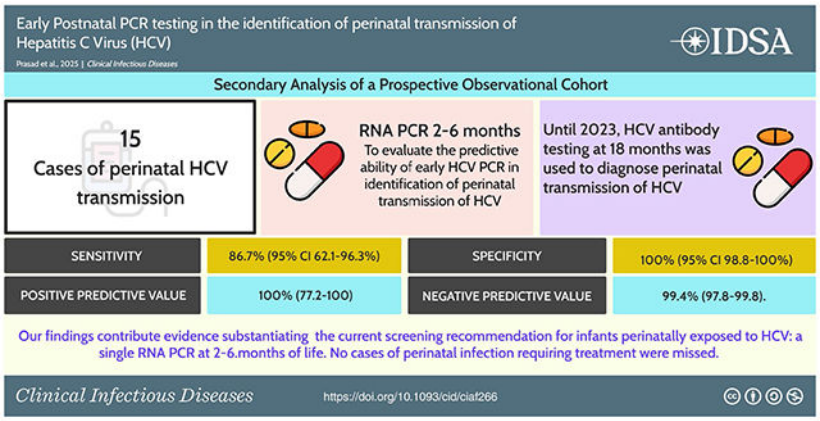
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Abstract

In this study, a single hepatitis C virus (HCV) RNA at 2–6 months was sensitive and specific (86.7% and 95% confidence interval [CI], 62.1%–96.3% and 100% and 95% CI, 98.8%–100%, respectively) in identifying perinatal transmission of HCV. No cases of perinatal infection requiring treatment were missed.

Graphical Abstract



Keywords

hepatitis C virus; HCV; perinatal transmission; PCR; pediatric screening

The World Health Organization has called for the elimination of hepatitis C virus (HCV) by 2030 [1]. In pursuit of that goal, there has been a focus on identification and linkage to treatment of birthing persons and their children [2]. Universal screening is now recommended in each pregnancy [3], contributing to the identification of pregnant adults with HCV. However, identification of children with perinatally acquired HCV has proven to be difficult. Until October 2023, at-risk children were not screened until age 18 months for

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perinatal HCV with an anti-HCV antibody test [4, 5]. As a result, children with perinatal HCV exposure often did not undergo the recommended testing to determine whether perinatal transmission occurred, resulting in a delay in diagnosis and linkage to care [6–10]. Under these guidelines, only 30% of at-risk children were appropriately tested [11]. Follow-up is known to be particularly difficult in this population who are also likely to be impacted by opiate use disorder. In addition to traditional barriers, such as transportation, time constraints, and family stresses, this population may have additional challenges including perceived stigmatization and discrimination, feeling overwhelmed secondary to the stress of parenting while engaging in substance use treatment, or feeling guilty, judged, or removed from the care of their child [12]. With these challenges, it stands to reason that the time between birth and 18 months is too large a gap to ensure that appropriate testing for children with perinatal HCV exposure is performed [2, 13].

Optimal identification of children with perinatal HCV infection will only be successful if strategies address and overcome barriers to screening. Loss to follow-up is a critical barrier to overcome. In an attempt to address this barrier, the Centers for Disease Control and Prevention (CDC) revised screening guidelines in 2023. Specifically, instead of HCV antibody screening at 18 months, the CDC now recommends a single HCV RNA test at age 2–6 months [11]. There are many reasons this strategy was supported, including more infants receive well-child visits at 2–6 months relative to children receiving testing at 18 months, early diagnosis of perinatal HCV transmission at age 2–6 months was determined to be cost-effective and cost-saving in preventing morbidity and mortality from chronic hepatitis C complications, and curative treatment is available starting at age 3 years. However, there is currently only a single study that offers sensitivity and specificity data to support the recommendation [14], suggesting that more evidence is necessary. Thus, our objective in this study was to evaluate the ability of early postnatal polymerase chain reaction (PCR) testing to identify perinatal transmission of HCV and perinatal HCV infection in a large prospectively ascertained cohort.

METHODS

This is a secondary analysis of a multicenter observational study of HCV in pregnancy [2]. Gravid individuals were eligible if they were found to be antibody-positive for HCV. To evaluate the predictive ability of early HCV PCR testing, only infants with both 2–6-month HCV PCR and ≥18-month HCV antibody or PCR results were included. We calculated sensitivity, specificity, positive and negative likelihood ratios, and positive and negative predictive values. As defined in our previous work, perinatal transmission of HCV was defined as either an infant who demonstrated HCV RNA at age 2–6 months or was found to be HCV RNA or antibody positive at 18–24 months of life. Sensitivity was defined as the proportion of children who demonstrated anti-HCV antibodies and/or were PCR-positive at ≥18 months and were PCR-positive at 2–6 months. Specificity was defined as the proportion of infants who were anti-HCV or PCR-negative at ≥18 months and were PCR-negative at 2–6 months. Confidence intervals (CIs) for specificity and sensitivity were calculated based on the Wilson score method and for likelihood ratios based on bootstrapping methods [15].

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RESULTS

Of 772 children with perinatal HCV exposure, 333 (43%) had HCV laboratory results at both 2–6 months and ≥18 months (Figure 1). Of those 333 children, 13 (4%) had a positive PCR test at 2–6 months, of whom 13 were confirmed HCV-positive at ≥18 months. Of the remaining 320 children with a negative PCR test at 2–6 months, 318 were confirmed to be anti-HCV–negative and 2 were anti-HCV–positive at ≥18 months. These 2 children were PCR-negative at 18 months. Thus, the specificity and sensitivity of early postnatal PCR testing was 100% (95% CI, 98.8%–100%) and 86.7% (95% CI, 62.1%–96.3%), respectively. Values were as follows: positive likelihood ratio, infinity (97.1–infinity); negative likelihood ratio, 0.13 (0–0.34); positive predictive value, 100% (77.2%–100%); negative predictive value, 99.4% (97.8%–99.8%). A post hoc sensitivity analysis was performed that included the 2 children who were anti-HCV–positive and PCR-negative as part of the HCV-negative group, as they clinically would not require treatment for HCV. This post hoc analysis yielded a sensitivity of 100% (95% CI, 77.2%–100.0%) and specificity of 100% (95% CI, 98.8%–100.0%).

DISCUSSION

Screening guidelines for children exposed to HCV have recently changed, supported by a single but compelling study. The previous study conducted at a children's hospital showed that a single PCR test for HCV RNA at 2–6 months had sensitivity of 100% (95% CI, 87.5%–100%) and specificity of 100% (95% CI, 98.3%–100%) for the diagnosis of perinatally acquired HCV [14]. Our findings enhance current CDC recommendations for children perinatally exposed to HCV. Our work demonstrates sensitivity and specificity similar to those estimated by Gowda et al for the ability of early HCV RNA testing to diagnose perinatally acquired HCV infection. By our case definitions, our sensitivity is less than previously demonstrated, but case definitions and clinical utility are likely different. We noted that 2 children in our cohort were HCV antibody–positive at 18 months but PCR-negative. We know that these antibody tests were performed at 18 months exactly, and no follow-up antibody was available to us. Additionally, no repeat PCR testing was available to lend insight. It is possible that the infants were exposed to RNA early, cleared the virus, and developed HCV antibody in response. Consistent with published experience, an alternative notion is that this could represent persistently circulating maternal antibody [14, 16]. Depending on the natural history, whether or not the antibody present at 18 months demonstrates perinatal transmission or persistent maternal antibody is debatable. Clinically, this distinction is insignificant given that in the absence of circulating RNA, no child in this cohort who required treatment for perinatal infection was missed using a single RNA test at 2–6 months. In addition, no child would have been prematurely dismissed from care based on the results of a 2–6-month PCR test. Future studies that focus on the fundamental differences in children, differences in perinatal exposures, or differences in long-term follow-up could shed light on the natural history of those children who were found to be RNA-negative at 2–6 months and HCV antibody–positive/RNA-negative at 18 months.

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Though limited by sample size, bias due to loss to follow-up, and availability of complete testing for the entire cohort, our findings contribute evidence to substantiate the current screening recommendation for children perinatally exposed to HCV. Ideally, earlier identification of children with perinatally acquired HCV will lead to improved linkage to care and ultimately cure. Ongoing surveillance will be necessary to evaluate the impact of this screening strategy and contribution to the goal of HCV elimination by 2030.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Potential conflicts of interest.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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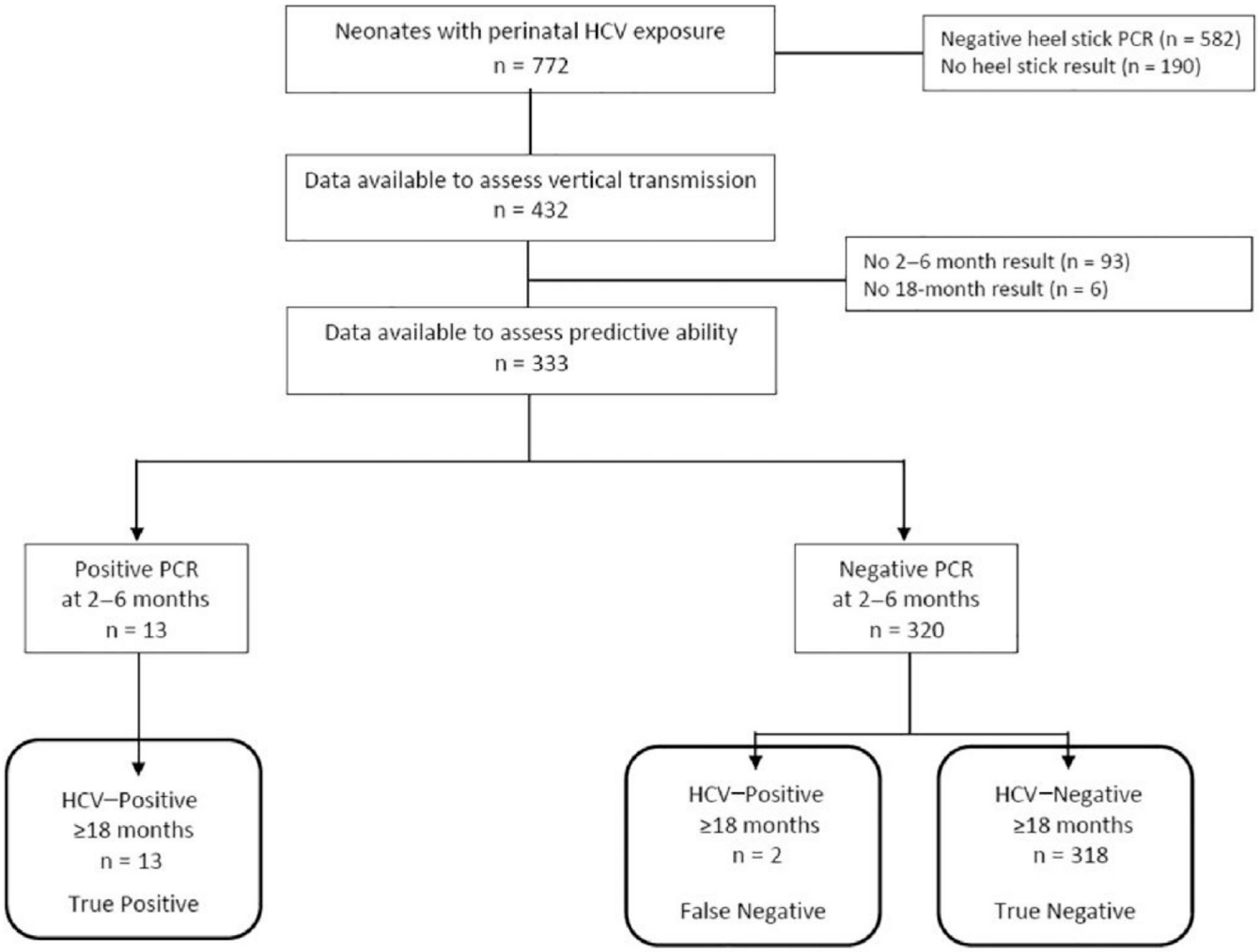


Figure 1.

Infant follow-up of HCV status [2]. False negatives were defined by case definition only. They were HCV PCR–negative, clinically negative, and would not require treatment. Abbreviations: HCV, hepatitis C virus; PCR, polymerase chain reaction.