

# Hepatitis C Virus Screening Among Children Exposed During Pregnancy

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abstract

**OBJECTIVES:** Because of the opioid epidemic, hepatitis C virus (HCV) infection is increasing among pregnant women, resulting in an increased risk of perinatal transmission and HCV infection among children. Our primary objectives in this study were to determine the prevalence of HCV among pregnant women and the frequency of pediatric HCV screening.

**METHODS:** A population-based, retrospective cohort of pregnant women who delivered between 2006 and 2014 was identified and classified as HCV infected or HCV uninfected by billing codes. Infant records linked to the HCV-infected pregnant women were identified and queried for HCV tests and the receipt of well-child services, which were defined as the presence of hemoglobin and/or lead testing at or after 9 months of age.

**RESULTS:** Between 2006 and 2014, 1043 (1.2%) HCV-infected pregnant women delivered, and the HCV prevalence increased by 60%. HCV-infected women were more likely to be <30 years of age (67% vs 53%;  $P < .001$ ), white (93% vs 72%;  $P < .001$ ), insured by Medicaid (77% vs 29%;  $P < .001$ ), and have opiate use disorder (68% vs 1%;  $P < .001$ ) than HCV-uninfected women. Infants born to HCV-infected women were more likely to be preterm (<37 weeks' gestation; 22% vs 10%;  $P < .001$ ) and of low birth weight (<2500 g; 23% vs 8%;  $P < .001$ ). Among 1025 HCV-exposed infants with available pediatric records, 323 (31%) received well-child services, and among these, only 96 (30%) were screened for HCV.

**CONCLUSIONS:** Despite the increased HCV prevalence among pregnant women and the risk of perinatal HCV transmission, HCV-exposed infants are not adequately screened, and many pediatric HCV infections remain undetected.



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Dr Chappell conceptualized and designed the study and drafted the initial manuscript; Drs Krans, Hillier, and Bogen were involved in the conceptualization and design of the study; Dr Meyn and Mr Crowe conducted the data analysis; and all authors reviewed and revised the manuscript, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

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**WHAT'S KNOWN ON THIS SUBJECT:** Hepatitis C virus (HCV) infection is increasing among young adults because of the opioid epidemic. Of infants who are exposed during pregnancy, 4% to 8% will become infected.

**WHAT THIS STUDY ADDS:** In this retrospective cohort study, the rate of HCV infection among pregnant women increased by 60%. Despite receiving well-child services, only 30% of infants who were exposed to HCV during pregnancy were screened for HCV infection.

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One of the most significant consequences of the opioid epidemic has been the rise in hepatitis C virus (HCV) infection among reproductive-aged persons who use intravenous drugs,<sup>1,2</sup> including pregnant women. A recent report revealed an 89% increase in HCV infection among pregnant women in the United States from 2009 to 2014.<sup>3</sup> Notably, HCV is transmitted from a pregnant woman to her infant in ~5.8% of cases.<sup>4</sup> In the United States, perinatal transmission is the primary cause of HCV infection in children. At least 40 000 children are exposed to HCV during pregnancy annually, resulting in an estimated 2700 to 4000 new cases of pediatric HCV infections each year.<sup>5,6</sup> As with hepatitis B infection, ~80% of children who acquired HCV infection through perinatal transmission develop chronic infection.<sup>7,8</sup> Although progression to severe liver disease may take decades, some children progress to cirrhosis more quickly.<sup>7,8</sup> Data from the Organ Procurement and Transplantation Network revealed that of the 5578 liver transplants performed in children ages 6 to 17 years from January 1, 1988, to July 31, 2017, 131 (2.3%) were in the setting of HCV infection.<sup>9</sup>

All infants born to women with HCV infection should be screened for HCV to evaluate for perinatal transmission.<sup>10</sup> The diagnosis of HCV in children is complicated by the passive placental transfer of maternal HCV immunoglobulin G antibodies to the infant. Because of the presence of these antibodies, HCV antibody testing before 18 months of age can lead to false-positive results. For this reason, the Centers for Disease Control and Prevention, the Infectious Diseases Society of America, and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition recommend in their pediatric HCV screening guidelines that an HCV antibody test be

performed at or after 18 months of age.<sup>10–12</sup> If a child's infection status is desired by the parents or screening provider before age 18 months, then HCV RNA detected by a polymerase chain reaction (PCR) test can be sent. However, an HCV RNA test is not the screening test of choice for perinatal HCV transmission and chronic pediatric HCV infection. Fluctuations in the levels of HCV viremia, especially in the first 18 months, are common and could lead to false-negative or false-positive results (spontaneous viral clearance).<sup>12–14</sup>

Several recent studies in the United States have revealed that despite these clear recommendations for screening, many HCV-exposed infants are not screened and many cases of HCV in children are not detected.<sup>15,16</sup> However, researchers in these studies did not assess whether decreased rates of screening among HCV-exposed infants were because of lapses in the receipt of well-child care or because of inadequate screening among children who were engaged in well-child services. Therefore, our objectives in this study were to determine the prevalence of HCV infection at a large, tertiary-care maternity hospital from 2006 to 2014 and the rate and type of pediatric HCV testing for HCV-exposed children who were engaged in well-child services. We also compared obstetric and neonatal outcomes among pregnant women with and without HCV.

## METHODS

After institutional review board approval from the University of Pittsburgh (PRO16020401), a retrospective cohort of women with singleton pregnancies delivering between January 1, 2006, and December 31, 2014, was identified by using the Magee Obstetric Maternal and Infant database, which contains information on all births at Magee-Womens Hospital of the

University of Pittsburgh Medical Center (UPMC) from January 1, 1995, to the present. Demographic characteristics, maternal medical history, and obstetric and neonatal outcomes were extracted from the Magee Obstetric Maternal and Infant database, with maternal HCV infection being determined by *International Classification of Diseases, Ninth Revision* (ICD-9) codes (070.41, 070.44, 070.51, 070.54, 070.70, or 070.71). Women with multiple gestations or without known delivery outcomes were excluded from analysis. By using this HCV-infected maternal cohort, infant identifiers linked to maternal records were extracted by an honest broker affiliated with the Center for Assistance in Research using eRecord at the UPMC, who extracted and deidentified all laboratory data up until September 21, 2016, for infants who were identified as being HCV exposed. If a woman in the retrospective cohort had >1 child over the study period, only the first child born during the study period was included in the analysis.

Magee-Womens Hospital of UPMC is a large, tertiary-care referral hospital, and many infants likely receive pediatric care outside of the UPMC system after delivery. Therefore, we identified a cohort of infants who received well-child services within the UPMC system. The receipt of well-child services was defined as the presence of lead and/or hemoglobin testing at or after 9 months of age in the UPMC medical record. Children who received well-child services in the UPMC system but did not have an HCV test performed (either HCV antibody testing or HCV RNA) were considered to be unscreened for HCV. The HCV screening test was defined as the first HCV test performed on each infant. Optimal screening for perinatal HCV transmission was defined as the HCV screening test being (1) an HCV RNA before 18 months of age or (2) an HCV

antibody test after 18 months of age. Infants with both HCV antibody and RNA tests sent simultaneously were considered to have optimal screening. Suboptimal HCV screening was defined as an HCV antibody test being sent before 18 months of age or an HCV RNA test being conducted after 18 months of age. Although a negative HCV antibody test result before 18 months of age is sufficient to rule out HCV, a positive HCV antibody result before 18 months of age cannot be used to distinguish maternal antibody contamination from perinatal HCV transmission. An HCV RNA test conducted after 18 months of age was considered suboptimal because the current pediatric HCV guidelines state that an HCV antibody test performed after 18 months of age is more diagnostically accurate and cost-effective compared with an HCV RNA test.<sup>10–12</sup> Children who had a negative HCV antibody screening test result at any age or 2 negative HCV RNA test results were considered to be negative for HCV infection. Children who had a positive HCV antibody result or an HCV RNA test after 18 months of age were considered to be positive for HCV infection. Children with only a single negative HCV RNA test result without any other follow-up testing were considered to have an indeterminate test because of Centers for Disease Control and Prevention, Infectious Diseases Society of America, and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition recommendations that a single negative HCV RNA result be followed by additional testing to confirm it.<sup>10–12</sup> Likewise, a child with a positive HCV antibody test result before 18 months of age was also considered to have an indeterminate test result. Children with tests ordered but no results were considered to have HCV screening but indeterminate HCV screening test results. The rate of perinatal transmission was determined among infants with determined HCV status

who also received well-child services in the UPMC system.

The change in HCV prevalence among pregnant women delivering at Magee-Womens Hospital of UPMC by year between 2006 and 2014 was evaluated by using  $\chi^2$  tests for linear trend. Demographic characteristics and obstetric and neonatal outcomes were compared between women with and without HCV by using Fisher's exact tests. Fisher's exact tests were also used to evaluate associations of maternal and neonatal characteristics with the presence or absence of pediatric HCV testing. Statistical analyses were performed by using SPSS statistical software release 23.0 (IBM Corporation, Armonk, NY), and all tests were evaluated at the 2-sided, .05 significance level.

## RESULTS

### Prevalence of HCV Infection Among Pregnant Women

Between January 1, 2006, and December 31, 2014, 87 924 pregnant women delivered at our institution who met the study criteria, and of those, 1043 (1.2%) were identified as having HCV infection. Demographic and obstetric characteristics of women with and without HCV infection are compared in Table 1. HCV-infected women were more likely to be <30 years of age (67% vs 53%;  $P < .001$ ), white (93% vs 72%;  $P < .001$ ), have Medicaid (77% vs 29%;  $P < .001$ ), have opiate use disorder (68% vs 1%;  $P < .001$ ), and have other substance use (11% vs 0.4%;  $P < .001$ ) than HCV-uninfected women. Infants born to HCV-infected women were more likely to be born preterm (<37 weeks' gestation; 22% vs 10%;  $P < .001$ ) and require care in the NICU (52% vs 12%;  $P < .001$ ). Over the 9-year study duration, the rate of HCV infection among women delivering at Magee-Womens Hospital of UPMC increased by 60% from 1026 per 100 000 women in

2006 to 1637 per 100 000 women in 2014 ( $P < .001$ ; Fig 1).

### Pediatric HCV Screening

Of the 1043 infants born to women with HCV infection, 1025 (98.2%) had data available in the electronic medical record system. Of 1025 HCV-exposed infants, 323 (32%) received routine lead and/or hemoglobin testing, which revealed that they were receiving well-child care in our system. Specifically, 207 (64%) had hemoglobin and lead testing, 105 (33%) had only hemoglobin testing, and 11 (3%) had only lead testing. Of those 323 who were identified as receiving well-child care, only 96 (30%) were tested for HCV. Of the tests conducted in those 96 infants receiving well-child care and HCV screening tests, 71 (74%) were HCV antibody tests, 22 (23%) were HCV PCR tests, and 3 (3%) were both HCV antibody and HCV PCR tests simultaneously. Among 96 children screened, 73 (76%) received an optimal initial HCV screening test. Suboptimal HCV screening evaluations for the remaining 23 children resulted because 11 (48%) HCV antibody tests were sent before 18 months of age and 12 (52%) HCV PCR tests were sent after 18 months of age (Fig 2). Infants whose mothers had an ICD-9 diagnosis of opioid use disorder were more likely to have been HCV tested (Table 2). There were no other maternal or infant risk factors identified to be positively or negatively associated with pediatric HCV screening. Of 702 infants who were not identified as receiving well-child care, 32 (5%) received HCV testing, 28 (87.5%) had HCV antibody testing performed, and 4 (12.5%) received HCV RNA testing, and of those tests, 22 (69%) were optimal (Fig 2).

### Perinatal HCV Transmission

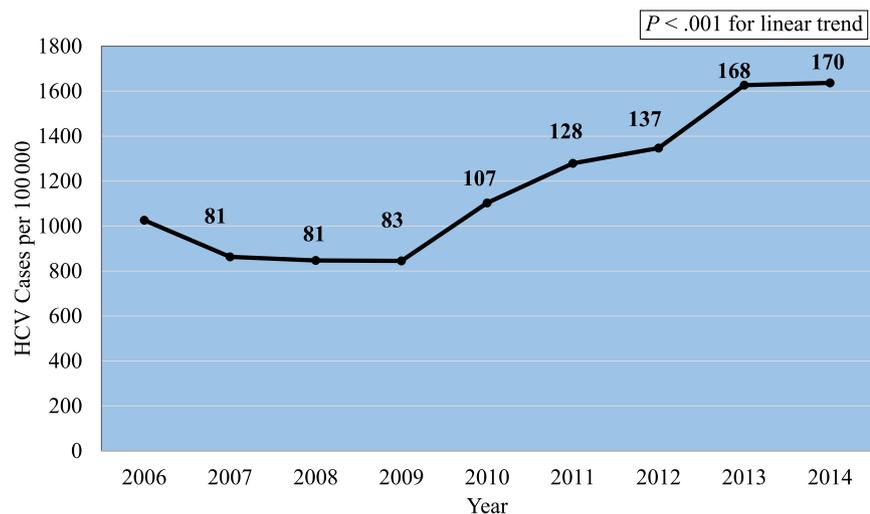
In the 96 infants who received both well-child care and HCV testing, 13 (14%) tests were inconclusive.

**TABLE 1** Characteristics of Women With and Without HCV Infection (N = 87 924)

	HCV-Negative (N = 86 881), n (%)	HCV-Positive (N = 10 443), n (%)	P <sup>a</sup>
Maternal age at delivery, y			
≥30	41 180 (47)	345 (33)	<.001
25–29	24 274 (28)	391 (38)	
<25	21 404 (25)	307 (29)	
Insurance			
Medicaid	25 472 (29)	806 (77)	<.001
Private	61 015 (70)	225 (22)	
Self-pay	394 (0.5)	12 (1)	
Race			
White	62 677 (72)	969 (93)	<.001
African American	17 204 (20)	55 (5)	
Other	3 679 (4)	3 (0.3)	
Unknown	3 321 (4)	16 (2)	
Married	50 527 (58)	130 (13)	<.001
Tobacco use	10 277 (12)	682 (65)	<.001
Opiate use disorder	1 183 (1)	712 (68)	<.001
Other substance use	340 (0.4)	111 (11)	<.001
Hepatitis B infection	117 (0.1)	10 (1)	<.001
HIV infection	69 (0.1)	5 (0.5)	.002
Vaginal delivery	62 472 (72)	717 (69)	.03
Gestational age, wk			
≥37	75 813 (87)	806 (77)	<.001
35–36	4 695 (5)	108 (10)	
<35	4 655 (5)	120 (12)	
NICU stay, d			
0	65 019 (75)	331 (32)	<.001
1–7	6 497 (8)	352 (34)	
≥8	3 860 (4)	192 (18)	

Less than 5% of data were missing for all variables.

<sup>a</sup> Fisher's exact test.

**FIGURE 1**

Prevalence of HCV in women delivering at Magee-Womens Hospital of UPMC (cases per 100 000 and total numbers per year from 2006 to 2014).

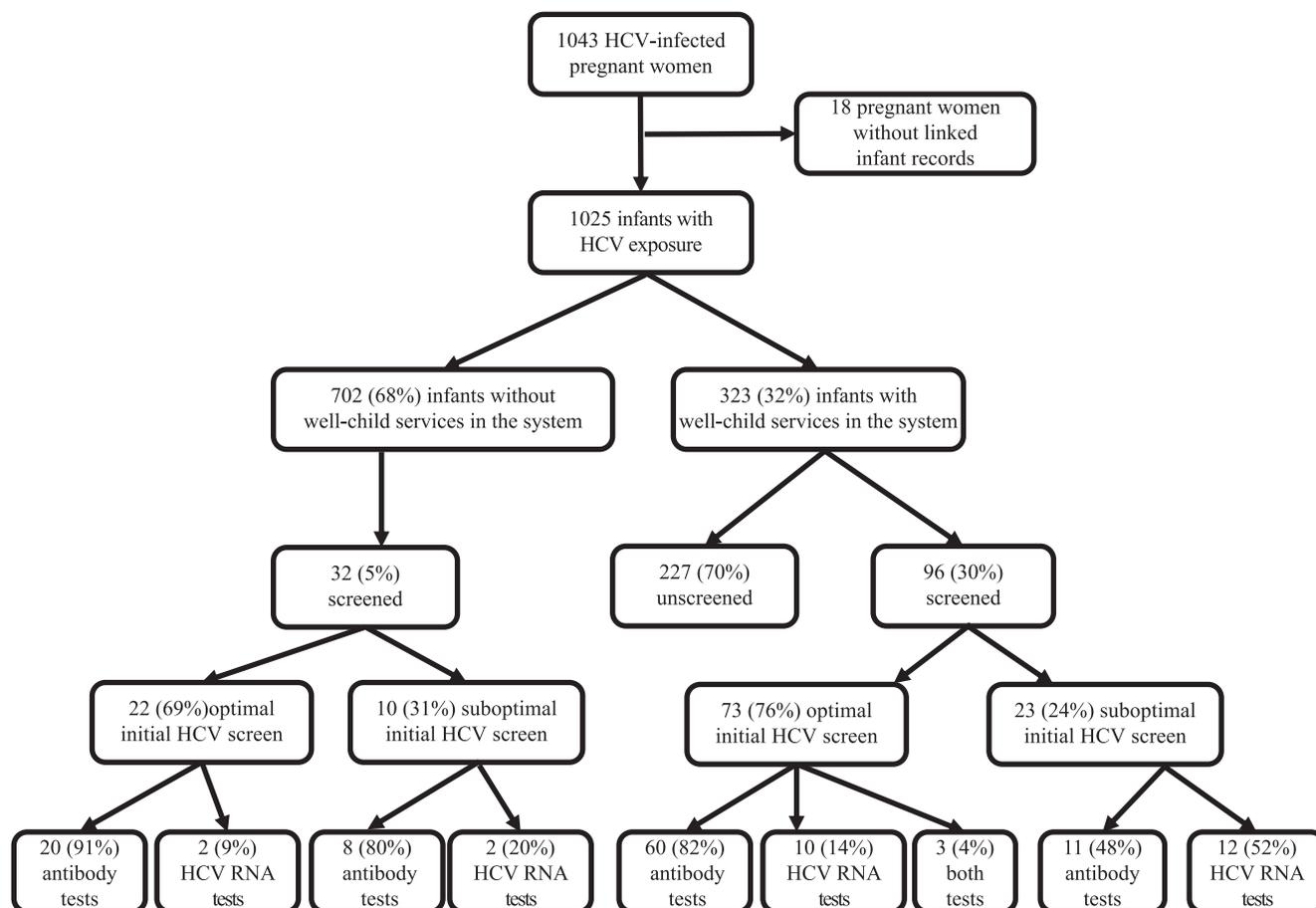
Three HCV RNA tests were ordered, but the results could not be found; 2 HCV antibody tests (positive results) performed before age 18 months (ages 13 and 6 months) were not repeated, and 8 HCV RNA tests were

sent in the first 18 months of life and were not repeated. Evidence of perinatal transmission, which is defined as a positive antibody result and/or a detectable HCV RNA result at or after 18 months of age, was

present in 7 (8.4%) of the 83 exposed children receiving well-child care and with interpretable HCV test results. Of these 7 HCV-infected children, only 3 had optimal screening tests. There were 2 additional cases of HCV infection identified among the 32 children screened for HCV who were not identified as receiving well-child care in our health system. Of the 9 children with evidence of perinatal transmission, 7 (78%) had HCV viremia (chronic HCV infection). Two of the 9 children had a positive HCV antibody test result, but 1 did not have an HCV RNA test sent, and the other had a negative HCV RNA test result, revealing a clearance of the HCV infection. Among the 7 children with confirmed chronic HCV infection (6 receiving well-child care in our system and 1 without), review of their laboratory data revealed that 5 had mild transaminase elevations (range aspartate aminotransferase: 54–106; alanine aminotransferase: 51–129), but none had evidence of liver disease, such as thrombocytopenia or abnormal coagulation tests. None of the HCV-infected children had an undetectable viral load or evidence of clearance or treatment during the study period; however, the children were young (20 months to 7 years of age) at the time of the most recent laboratory evaluation, and only 4 children had repeat testing done during the study period.

## DISCUSSION

The prevalence of HCV increased by 60% among women delivering at our institution from 2006 to 2014, particularly among those who are younger, white, Medicaid insured, and who have a history of opioid abuse. Importantly, despite receiving other well-child services, infants who were exposed to HCV at birth are screened at a low rate of only 30%. Of the infants tested with conclusive results, the HCV transmission rate



**FIGURE 2**  
Frequency and quality of pediatric HCV screening.

was 8.4%, with 7.2% having chronic HCV infection, which is consistent with the 5.8% (95% confidence interval 4.2%–7.8%) rate previously reported.<sup>4</sup> Without appropriate screening, children who are at risk for perinatal transmission may remain undiagnosed until they become symptomatic or have abnormal liver enzyme levels found incidentally. Delays in diagnosis could lead to delays in appropriate referrals and curative treatment or irreversible liver disease, such as cirrhosis or hepatocellular carcinoma. Additionally, only opioid use disorder was positively associated with pediatric HCV screening being identified, revealing that additional risk factors (eg, substance use) may prompt providers to screen infants for HCV infection.

There are several limitations to our study. ICD-9 diagnostic codes were used for case identification of HCV in our cohort of pregnant women, which may have resulted in underreporting or inaccuracies in the diagnosis of HCV. Second, our data set represents a single academic, tertiary-care medical center. Third, some infants receiving well-child care could have moved out of the area and received HCV screening outside of our system. However, our health system includes 30 hospitals and 41% of the medical-surgical market share in the greater western Pennsylvania area (29 counties),<sup>17</sup> which minimizes missing data because of patient migration. Additionally, laboratory results from external or hospital-based laboratories are also included in our electronic health record. Finally, we identified children as having

received primary pediatric care in our health system using the presence of hemoglobin and lead testing. Although this is not the only way to identify pediatric primary care, we used this approach because it was evidenced that children had blood obtained for screening at ~1 to 2 years of age.

Consistent with previous reports, we found a significant increase in the prevalence of HCV infection among pregnant women. Researchers in a recent report noted an 89% increase in the prevalence of HCV among delivering women nationally from 2009 to 2014, with a 163% increase in Tennessee.<sup>3</sup> Others have noted a >200% increase in HCV detection among women of reproductive age in Kentucky and an increased HCV incidence among people age

**TABLE 2** Maternal Risk Factors That Are Predictive of Pediatric HCV Screening (*N* = 323)

	HCV Unscreened ( <i>N</i> = 227), <i>n</i> (%)	HCV Screened ( <i>N</i> = 96), <i>n</i> (%)	<i>P</i> <sup>a</sup>
Maternal age at delivery, y			
≥30	70 (31)	35 (37)	.58
25–29	96 (42)	39 (41)	
<25	61 (27)	22 (23)	
Insurance			
Medicaid	177 (78)	74 (77)	.78
Private	49 (22)	21 (22)	
Self-pay	1 (0.4)	1 (1)	
Race			
White	207 (91)	93 (97)	.34
African American	14 (6)	3 (3)	
Other	1 (0.4)	0 (0)	
Unknown	5 (2)	0 (0)	
Tobacco use	149 (66)	75 (78)	.08
Opioid use disorder	142 (63)	73 (76)	.02
Other substance use	30 (13)	6 (6)	.08
Maternal education			
Some college or graduate	75 (33)	35 (37)	.64
High school graduate	90 (40)	38 (40)	
Less than high school graduate	32 (14)	15 (16)	
Unknown	30 (13)	8 (8)	
Birth wt, g			
≥2500	173 (76)	78 (81)	.60
1500–2499	45 (20)	17 (18)	
<1500	8 (4)	1 (1)	

<sup>a</sup> Fisher's exact test.

<31 years in a nonurban setting with a history of intravenous drug use.<sup>1,2</sup> Likewise, in our study, 68% of HCV-infected pregnant women had a current diagnosis of opioid use disorder.

Despite the increasing HCV prevalence among women of reproductive age, there are few studies in which researchers evaluate the screening of infants who are perinatally exposed to HCV. Researchers in 1 study from Florida made estimates based on the prevalence of HCV infection among Florida residents and reported that only 11.7% of expected pediatric cases of HCV had been identified by laboratory testing.<sup>16</sup> A recent study by the Philadelphia Health Department noted that only 16% of 537 infants exposed to HCV at birth were appropriately screened for HCV at any time after 18 months of age.<sup>15</sup> Although the researchers in these studies report a low HCV screening prevalence among children, they did

not evaluate for well-child health care engagement and did not account for the recommended window for HCV screening. As such, we expand the knowledge of pediatric health services use for this population by determining that only 96 (30%) of 323 children who received well-child care, which included blood laboratory assessments, received any HCV screening. Moreover, of initial HCV screening tests sent, 76% were optimal per the screening guidelines.<sup>10–12</sup>

There are several possible reasons for the failure to adequately screen infants who are perinatally exposed to HCV. Information regarding maternal HCV diagnosis might not be accurately transferred to the pediatric record. If not transferred electronically, pediatric providers may fail to obtain accurate historical information regarding HCV risk exposures because parents may selectively disclose stigmatizing behaviors, such as past illegal

drug use. Additionally, because of the lack of universal screening during pregnancy, many pregnant women may not be screened during pregnancy and be unaware of their diagnosis. In an evaluation of HCV screening practices among 800 high-risk pregnant women with opioid use disorder, only 77% were evaluated for HCV infection during pregnancy.<sup>18</sup> Finally, HCV-infected pregnant women may not receive adequate counseling by obstetric and primary care providers regarding the risk of perinatal HCV transmission and the need for postnatal HCV screening.

The past decade has brought a revolution in the management of HCV, with 3 Food and Drug Administration–approved drug combinations that have demonstrated >95% efficacy in curing HCV in 8 to 12 weeks of oral once-daily therapy.<sup>19–21</sup> Because of the safety profile of these agents, some of these antiviral combinations are currently being evaluated for use in pregnant women<sup>22</sup> and pediatric populations.<sup>23</sup> Currently, the treatment of HCV-infected children is deferred until 12 years of age because the directly acting antiviral agents are only Food and Drug Administration–approved for children aged ≥12 years; however, there are 5 studies in preparation or in which researchers are actively recruiting children as young as 3 years to evaluate the safety and efficacy of HCV treatment (clinicaltrials.gov identifiers: NCT03022981, NCT03379506, NCT02249182, NCT03379506, and NCT03067129). Given that spontaneous clearance of HCV is more likely to occur before 36 months of age,<sup>7,24</sup> it is prudent to wait until 3 years of age for treatment implementation.<sup>12</sup>

Programs that are focused on identifying pregnant women with HCV infection during prenatal care and diagnosing HCV-infected

infants are critical to the prevention of the long-term sequelae of HCV infection, particularly now that there are increasingly easy and better-tolerated HCV treatments available for children. The near elimination of the perinatal transmission of HIV required routine screening and aggressive antiviral therapy.<sup>25</sup> The emerging data from our study reveal that the epidemic of HCV in pregnant women is growing and that most perinatally infected children are not being identified, impeding linkage to care.

Given the difficulties involved with risk-based screening and the increasing prevalence of HCV among pregnant women, consideration should be given to the evaluation and implementation of universal HCV screening during pregnancy, especially in high-prevalence areas. Additionally, because of the poor rates of pediatric HCV screening described, future researchers should focus on interventions to increase screening in infants who are at risk for perinatal HCV acquisition by including technology to improve the

transfer of maternal HCV status to the pediatric record and increase pediatric provider awareness regarding HCV screening guidelines.

#### ABBREVIATIONS

HCV: hepatitis C virus  
 ICD-9: *International Classification of Diseases, Ninth Revision*  
 PCR: polymerase chain reaction  
 UPMC: University of Pittsburgh Medical Center

Research Institute from Merck, and Dr Hillier has served as a consultant for Merck. Mr Crowe and Dr Meyn have indicated they have no financial relationships relevant to this article to disclose.

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