Outcomes of Infants Born to Women Infected With Hepatitis B

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abstract

BACKGROUND AND OBJECTIVES: Perinatal exposure is an important mode of hepatitis B virus (HBV) transmission, resulting in chronic disease in ~90% of infected infants. Immunoprophylaxis recommended for infants born to hepatitis B surface antigen–positive mothers reduces up to 95% of perinatal HBV infections. We sought to identify factors associated with perinatal HBV transmission.

METHODS: We analyzed prospectively collected data from 5 of 64 US-funded Perinatal Hepatitis B Prevention Programs during 2007–2013. We examined effects of maternal demographic and laboratory results, infant gestational age and birth weight, and immunoprophylactic management on perinatal HBV infection.

RESULTS: Data from 17 951 mother-infant pairs were analyzed. Among 9252 (51.5%) infants for whom hepatitis B surface antigen testing results were available, 100 (1.1%) acquired perinatal HBV infection. Both hepatitis B (HepB) vaccine and hepatitis B immune globulin were administered within 12 hours of birth for 10 760 (94.9%) of 11 335 infants with information. Perinatal HBV infection was associated with younger maternal age (P = .01), Asian/Pacific Islander race ($P < .01$), maternal hepatitis B e-antigen positivity ($P < .01$), maternal antibody to hepatitis B e-antigen negativity ($P < .01$), maternal viral load ≥2000 IU/mL (P = .04), and infant receipt of <3 HepB vaccine doses (P = .01). Four infants born to 429 mothers with viral load testing were infected; all 4 were born to mothers with viral loads in the ninth or tenth decile.

CONCLUSIONS: Perinatal HBV infection occurred among 1% of infants, most of whom received recommended immunoprophylaxis. Infants at greatest risk of infection were those born to women who were younger, hepatitis B e-antigen positive, or who had a high viral load or those infants who received <3 HepB vaccine doses.

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Dr Schillie performed the analyses and drafted and revised the manuscript; Ms Walker designed data collection instruments, coordinated data collection at 5 sites, managed and analyzed data, and critically reviewed the manuscript; Mr Veselsky coordinated data collection at 5 sites and critically reviewed the manuscript; Ms Crowley, Ms Dusek, Ms Lazaroff, Ms Morris, and Mr Onye supervised data collection at individual sites; Drs Ko and Nelson and Ms Fenlon critically reviewed the manuscript; Dr Murphy conceptualized the study and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Timely immunoprophylaxis and completion of the 3-dose hepatitis B vaccine series represents the cornerstone of perinatal hepatitis B prevention. Immunoprophylaxis for infants born to hepatitis B surface antigen–positive mothers reduces up to 95% of perinatal hepatitis B virus infections.

WHAT THIS STUDY ADDS: Despite recommended immunoprophylaxis, perinatal hepatitis B virus infection occurs among ~1% of infants. Infants born to mothers who are younger, hepatitis B e-antigen positive, or who have a high viral load or infants who receive <3 hepatitis B vaccine doses are at greatest risk of infection.

Approximately 1 million persons in the United States have chronic hepatitis B virus (HBV) infection, and 5000 to 8000 additional persons become chronically infected annually.[1,2] An estimated 25 000 infants are born to mothers positive for hepatitis B surface antigen (HBsAg) in the United States each year.[3] Perinatal exposure, either in utero or during delivery, is an important mode of HBV transmission.[4] Approximately 90% of HBV-infected infants will develop chronic infection,[5–7] with an ensuing 25% risk of premature death from liver failure or hepatocellular carcinoma.[6,7]

For infants born to HBsAg-positive women, immunoprophylaxis is reported to be 85% to 95% effective in preventing perinatally acquired chronic HBV infection.[8,9] The Advisory Committee on Immunization Practices (ACIP) recommends immunoprophylaxis consisting of hepatitis B (HepB) vaccine and hepatitis B immune globulin (HBIG) within 12 hours of birth, followed by completion of a HepB vaccine series (≥3 doses for infants with a birth weight ≥2000 g; ≥4 doses for infants with a birth weight <2000 g), and postvaccination serologic testing for vaccine-induced antibody and HBV infection.[8] Through grants to public health immunization programs, US Perinatal Hepatitis B Prevention Programs (PHBPPs) were created by the Centers for Disease Control and Prevention (CDC) in 1990 to accelerate progress toward elimination of perinatal HBV infection.[6] PHBPPs in 64 public health jurisdictions in the United States, its territories, and independent island nations identify pregnant HBsAg-positive women and ensure their infants receive timely immunoprophylaxis, including postvaccination serologic testing.[8] The CDC provided additional funding for 3 PHBPPs from 2007 to 2012 and for 2 PHBPPs from 2008 to 2012 to evaluate maternal, infant, and immunoprophylaxis management characteristics and outcomes of infants born to HBsAg-positive mothers.[3] PHBPPs with ≥400 births to HBsAg-positive women annually were eligible to apply for this additional funding; awardees each received $100 000 per year, which could be used to coordinate or enhance data collection. In this article, we describe perinatal HBV infection status among infants born to HBsAg-positive mothers from these 5 Enhanced PHBPP (EPHBPP) sites.

METHODS

Data Source

HBsAg-positive pregnant women were identified through PHBPP activities.[6] Program staff at the 5 EPHBPP sites (Florida, Michigan, Minnesota, New York City, and Texas [excluding cities of Houston and San Antonio]) collected data on maternal demographic and laboratory test results, infant gestational age and birth weight, immunoprophylactic management, and infant serologic outcomes, which were then submitted to the CDC. For the current analysis, data for mother-infant pairs reported by EPHBPP sites to the CDC from January 2008 through March 2013 were included. The study consisted of an analysis of existing data and was determined by the CDC to be exempt from review by an institutional review board.

Measures

Pregnant/postpartum women were eligible for EPHBPP enrollment if they were HBsAg-positive. Perinatal HBV infection was defined as HBsAg positivity in an infant <24 months of age born to an HBsAg-positive woman, regardless of the infant's antibody to hepatitis B surface antigen (anti-HBsAg) test result. Infant infection status was deemed unknown when HBsAg test results were missing or indeterminate.

Maternal age at the estimated date of delivery was categorized as follows: <25 years, 25 to 29 years, 30 to 34 years, and ≥35 years; maternal ages <8 years or >54 years were deemed biologically implausible and recoded as missing. Maternal race/ethnic combinations of black Hispanic and white Hispanic were combined and recoded as Hispanic. Race/ethnicity was analyzed according to 5 categories: Asian/Pacific Islander, black non-Hispanic, white non-Hispanic, Hispanic, and other (including Alaskan Native/Native American) as reported by the health care provider or PHBPP case manager. Maternal place of birth and primary language were dichotomized as US-born and foreign-born and English and non-English, respectively.

Maternal laboratory test results included hepatitis B e-antigen (HBeAg), antibody to hepatitis B e-antigen (anti-HBe), and viral load. Results obtained >1 year before the estimated date of delivery or >30 days after the estimated date of delivery were recoded as missing. Unknown and indeterminate values were also recoded as missing. A viral load of 2000 IU/mL was considered equivalent to 10 000 copies/mL and 3.3 log IU/mL.[10] Viral load was dichotomized as ≥2000 IU/mL and <2000 IU/mL in accordance with previous studies defining viral load thresholds.[11,12] Viral load was recoded as missing when reported in unknown units or in units other than IU/mL, copies/mL, or log IU/mL. Categories of viral load deciles were calculated for viral load values within each category of viral load units (IU/mL, copies/mL, or log IU/mL).

Gestational age was calculated on the basis of the number of days between the estimated date of delivery and date of birth. The estimated date of delivery was assumed to correspond to 40 weeks of gestation. Gestational ages calculated as older than 30 days beyond the estimated date of delivery or younger than 150 days before the

estimated date of delivery were deemed biologically implausible and recoded as missing. Gestational age was dichotomized as <37 weeks and ≥37 weeks. Infant birth weight was collected dichotomously as either <2000 g or ≥2000 g; unknown infant birth weight was recoded as missing.

The timing of administration of the birth dose of HepB vaccine and HBIG was recoded as missing when either date or time of birth, date or time of HepB vaccine administration, or date or time of HBIG administration were unknown. The administration of HepB vaccine birth dose or HBIG recorded as ≥120 hours after birth was deemed erroneous and therefore recoded as missing. The timing of administration was dichotomized at ≤12 hours and >12 hours, consistent with ACIP recommendations.[8] Infants were considered to have received 3 HepB vaccine doses when any date was recorded for a third vaccine dose and were considered to have received <3 HepB vaccine doses when no date was recorded for a third vaccine dose.

Statistical Analysis

Statistical analyses were conducted by using SAS 9.3 (SAS Institute, Cary, NC). Mother-infant pairs were the unit of analysis. Bivariate analyses were performed to examine associations between maternal and infant characteristics and infant infection status by using either χ^2 (Mantel-Haenszel χ^2 for maternal age) or Fisher's exact tests.
A bivariate analysis was performed to examine HBeAg positivity by maternal age category by using the Mantel-Haenszel χ^2 test. P values <.05 were considered statistically significant.

RESULTS

The 5 EPHBPPs identified 17 951 mother-infant pairs (15 938 mothers). Median maternal age was 30.0 ± 5.5 years (range: 14.5–51.6 years). Most infants were born to Asian/Pacific Islander (61.2%, or 10 537 of 17 204 with information) and foreign-born (88.7%, or 14 516 of 16 374 with information) women. The pregnancy did not result in a live birth for 639 (5.0% of 12 775 with disposition information) mother-infant pairs.

The time of administration of the HepB vaccine birth dose and HBIG was known for 11 479 (63.9%) and 11 633 (64.8%) of 17 951 infants, respectively. HepB vaccine and HBIG were administered within 2 hours of birth for 5042 of 11 479 (43.9%) and 4273 of 11 633 (36.7%) infants, respectively, and within 12 hours of birth for 11 070 of 11 479 (96.4%) and 11 112 of 11 633 (95.5%) infants, respectively. Of the 11 335 infants with known time of administration for both HepB vaccine birth dose and HBIG, 10 760 (94.9%) were administered both HepB vaccine and HBIG within 12 hours of birth. Of the 6071 infants with birth weights ≥2000 g and HBsAg testing results reported, 6047 (99.6%) completed ≥3 HepB vaccine doses. Of the 1014 infants with birth weights <2000 g and HBsAg testing results reported, 178 (17.6%) and 1007 (99.3%) completed ≥4 HepB vaccine doses and ≥3 HepB vaccine doses, respectively.

Among the 9252 infants for whom HBsAg testing results were available, 100 (1.1%) acquired perinatal HBV infection. The number of HepB vaccine doses was associated with infant infection; 1.1%, or 97 of 9207 infants with ≥3 doses, developed infection on the basis of postvaccination testing, compared with 6.7% (3 of 45) of infants with <3 doses (P = .01) (Table 1). Fourteen of 71 infected infants with information weighed <2000 g at birth; 1 of these 14 infants received a fourth vaccine dose. None of the following were significantly associated with perinatal infection: timing of HepB vaccine birth dose (≤12 vs >12 hours), timing of HBIG administration (≤12 vs >12 hours), gestational age, or birth weight.

The proportion of infected infants decreased with increasing maternal age, from 1.8% (26 of 1422) among infants born to women aged <25 years to 0.9% (17 of 1875) among women aged ≥35 years (P = .01) (Table 1). The proportion of infected infants varied by maternal race/ethnicity (P < .01); Asian/Pacific Islander women delivered the greatest proportion of infected infants (1.4%, or 81 of 5833) whereas white, non-Hispanic women delivered the smallest proportion (0.1%, or 1 of 695). Foreign-born women and women whose primary language was not English delivered a greater proportion of infected infants (1.1% [87 of 7784] and 1.3% [63 of 4675], respectively), compared with US-born women (0.6% [5 of 795]; P = .20) and women whose primary language was English (0.8% [21 of 2771]; P = .02) (Table 1).

Overall, 35.8% (664 of 1884) mother-infant pairs with reported HBeAg results were HBeAg positive. Women positive for HBeAg delivered a greater proportion of infected infants than did those who were negative for HBeAg (3.2% [12 of 374] and 0.0% [0 of 772], respectively; P < .01), and women negative for anti-HBe delivered a greater proportion of infected infants than did women who were positive for anti-HBe (3.2% [6 of 190] and 0.2% [1 of 618], respectively; P < .01) (Table 1). The proportion of women positive for HBeAg decreased with increasing maternal age (Table 2). Asian/Pacific Islander women had the greatest prevalence of HBeAg positivity, whereas black non-Hispanic mothers had the lowest (43.7% [576 of 1319] vs 16.4% [67 of 408]; P < .01) (data not shown).

A greater proportion of infected infants were born to women with viral loads ≥2000 IU/mL compared with <2000 IU/mL (2.1% [4 of 188] and 0.0% [0 of 241], respectively;

TABLE 1 Factors Associated With Infection Status Among Infants Born to HBsAg-Positive Mothers

	Maternal-Infant Pairs With Available Information, *n* (%)	HBsAg-Positive Infants		HBsAg-Negative Infants		*P*
		n	%	*n*	%	
Overall	9252 (100)	100	1.1	9152	98.9	—
Maternal age	8827 (95.4)					.01
<25 years		26	1.8	1396	98.2	
25–29 years		32	1.1	2870	98.9	
30–34 years		23	0.9	2605	99.1	
≥35 years		17	0.9	1858	99.1	
Maternal race	9069 (98.0)					<.01
Asian/Pacific Islander		81	1.4	5752	98.6	
Black, non-Hispanic		11	0.5	2081	99.5	
White, non-Hispanic		1	0.1	694	99.9	
Hispanic		2	0.6	323	99.4	
Other (including AN/NA)		1	0.8	123	99.2	
Maternal place of birth	8579 (92.7)					.20
US-born		5	0.6	790	99.4	
Foreign-born		87	1.1	7697	98.9	
Maternal primary language	7446 (80.5)					.02
English		21	0.8	2750	99.2	
Non-English		63	1.3	4612	98.7	
Maternal HBeAg status	1146 (12.4)					<.01[a]
HBeAg-positive		12	3.2	362	96.6	
HBeAg-negative		0	0.0	772	100.0	
Maternal anti-HBe status	808 (8.7)					<.01[a]
Anti-HBe-positive		1	0.2	617	99.8	
Anti-HBe-negative		6	3.2	184	96.8	
Maternal viral load	429 (4.6)					.04[a]
≥2000 IU/mL		4	2.1	184	97.9	
<2000 IU/mL		0	0.0	241	100.0	
Maternal treatment during this pregnancy	7529 (81.4)					.05[a]
Treated for hepatitis B		6	2.6	229	97.5	
Not treated for hepatitis B		79	1.1	7215	98.9	
Gestational age	8736 (94.4)					.09
<37 weeks' gestation		13	1.8	730	98.3	
≥37 weeks' gestation		85	1.1	7908	98.9	
Infant birth weight	7085 (76.6)					.21
<2000 g		14	1.4	1000	98.6	
≥2000 g		58	1.0	6013	99.0	
Timing of vaccine birth dose	6270 (67.8)					.73[a]
Administered ≤12 hours		69	1.1	5987	98.9	
Administered >12 hours		1	0.5	213	99.5	
Timing of HBIG	6378 (68.9)					1.00[a]
Administered ≤12 hours		70	1.2	6040	98.9	
Administered >12 hours		3	1.1	265	98.9	
Number of vaccine doses	9252 (100)					.01[a]
≥3 doses		97	1.1	9110	99.0	
<3 doses		3	6.7	42	93.3	

AN, Alaska Native; NA, Native American.
[a] Fisher's exact test.

P = .04) (Table 1). Among the infants with known infection status for whom maternal viral load test results were available, the median maternal viral load was 1059 IU/mL (5870 copies/mL or 3.0 log IU/mL). Four of 429 (0.9%) infants born to women with viral load testing results were infected. One of these 4 infected infants received HBIG at 13 hours of life; otherwise, HepB vaccine and HBIG were administered within 12 hours of life. Two of the infected infants were born to women with viral loads in the ninth decile (64 054–37 980 028 IU/mL [550 001–203 700 000 copies/mL, or 5.4–8.2 log IU/mL]) and 2 were born to women with viral loads in the tenth decile. Viral load values for the mothers of these 4 infected infants were 8.1 log IU/mL, 100 000 000 copies/mL, 847 000 000 copies/mL, and 108 963 583 IU/mL.

DISCUSSION

Perinatal HBV infection occurred in slightly more than 1% of the 9252 infants born to HBsAg-positive women included in this analysis. Most infected and uninfected infants with birth weights ≥2000 g received ACIP-recommended immunoprophylaxis. Before the widespread availability of immunoprophylaxis, the proportion of infants born to HBsAg-positive women acquiring HBV infection was ~30% for infants born to HBeAg-negative women and 85% for infants born to HBeAg-positive women.[4,13]

Timely immunoprophylaxis and completion of the ACIP-recommended 3-dose HepB vaccine series is the cornerstone of perinatal hepatitis B prevention. In the United States, prophylaxis for infants born to HBsAg-positive women consists of HepB vaccine and HBIG administered within 12 hours of birth, followed by completion of the vaccine series and postvaccination testing for HepB vaccine–induced anti-HBsAg or infection.[8] When used alone, HepB vaccine and HBIG are 75% (41.7%–86.2%) and 71% effective in preventing perinatal HBV transmission, respectively.[7,14] Their combined efficacy was 94% considering infants born to HBsAg-positive women.[7]

We demonstrated that the number of HepB vaccine doses was associated with risk of infant infection; infection occurred in 6.7% (3 of 45 infants) of infants who received <3 doses, compared with 1.1% (97 of 9207 infants) of infants who received ≥3 doses (*P* = .01) (Table 1). Because 99.5% (9207 of 9252 infants) received ≥3 doses, the number of infants receiving <3 doses was comparatively small, possibly

TABLE 2 Maternal HBeAg Status by Maternal Age

Age	HBeAg-Positive	HBeAg-Negative
<25 years	165 (49.3)	170 (50.8)
25–29 years	262 (37.1)	445 (62.9)
30–34 years	167 (31.5)	363 (68.5)
≥35 years	80 (25.6)	232 (74.4)

Data are presented as *n* (%). $P < .0001$ (Mantel-Haenszel χ^2; includes mother-infant pairs in whom infant's HBsAg status is unknown).

hindering the interpretation of results. Fourteen of the 71 infected infants (19.7%) with information weighed <2000 g at birth; 13 of these 14 infants did not complete the ACIP-recommended 4 doses of HepB vaccine. Although the paucity of data for infants with birth weights <2000 g precluded assessing the impact of not receiving the recommended number of vaccine doses on transmission, further efforts to improve adherence with ACIP recommendations are warranted.

We found an increased risk of perinatal HBV transmission at younger maternal ages ($P = .01$). Younger women in the EPHBPP were more often HBeAg positive than were older women. It has been noted that HBeAg positivity declines during the childbearing years.[8,15] Studies among HBsAg-positive pregnant women in the United States have reported the prevalence of HBeAg positivity to be between 18.0% and 36.4%.[16–18] HBeAg positivity is a known risk factor for infectivity.[8] It is plausible that a greater prevalence of HBeAg positivity among younger women[19] accounts for the association between younger maternal age and perinatal transmission. Others have hypothesized that HBeAg positivity and longer labors among younger women could contribute to the increased transmission.[20]

Kohn et al[16] reported that black women infected with HBV were significantly less likely to be HBeAg positive compared with other races, and Ott et al[19] found that HBeAg positivity was highest in young infected females in East Asia and less common in sub-Saharan and North Africa. These results are consistent with our findings. Further analyses to ascertain differences in perinatal HBV transmission by race and country of birth, and possibly HBV genotype, may yield useful information.

We found a significantly greater proportion of infected infants born to women whose viral loads were ≥2000 IU/mL compared with viral loads <2000 IU/mL ($P = .04$). Although the majority of perinatal HBV infections are acquired during the birth process, an estimated 5% to 15% of perinatal infections occur from in utero transmission.[21] The risk of in utero infection increases linearly with increasing maternal viral load.[22] Although antiviral treatment during pregnancy may be indicated for chronic HBV infection in only a small proportion of women, antiviral treatment initiated on a short-term basis during pregnancy may be effective in preventing immunoprophylaxis failures in mothers with high viral loads,[4,23–25] although definitive results from clinical trials are still needed. Fan et al[26] recently reported that 12.6% (64 of 507) pregnant women with chronic hepatitis B received antiviral treatment. Testing HBsAg-positive mothers for viral load or HBeAg, and providing antiviral treatment of those who are HBeAg positive or who have high viral loads, can be cost-effective.[27]

Although previous studies have established an increased risk of perinatal HBV transmission with immunoprophylaxis delays, our data were too sparse to assess the effect of delayed prophylaxis on infection status. Marion et al[20] reported that timing of the HepB vaccine birth dose is an important predictor of infection risk, with the lowest risk among those vaccinated at <3 days of age compared with age ≥7 days. Beasley et al[7,28] demonstrated that HBIG is usually protective if administered within a few hours of birth with or without HepB vaccine, but found a marked decrease in efficacy when administration was delayed beyond 48 hours of life.[29,30] Because relatively few infants in the EPHBPP received immunoprophylaxis beyond 12 hours of life, we were precluded from analyzing the effect of more extreme delays of immunoprophylaxis administration (eg, vaccine and HBIG administered at 2 days of life) on infant infection status.

This report is subject to several limitations. Although the overall number of mother-infant pairs was large (>17 000), 48.5% (8699 of 17 951 infants) were not reported to have been tested for infection, possibly limiting the ability to detect significant associations. Our analysis on infant outcomes was limited to those infants who completed postvaccination serologic testing. Missing values included infants not yet born; data from these mother-infant pairs were included in analyses when possible. In addition, it is possible that there was a different incidence of perinatal infection among those infants whose test results were reported than those not reported, particularly if the maternal characteristics associated with higher infection rates were not evenly distributed across both groups. Previous analyses have revealed that many children without test results moved to China before completing the 3-dose series (J. L., New York City PHBPP surveillance data, 2011). Because their mothers are of Asian descent, a group that has been demonstrated to have a higher likelihood of HBeAg positivity, it is possible that there was greater transmission among the children whose test results were less likely to have been reported. Similarly, the small proportion of women with testing data further impeded some analyses. The paucity of these data prevented the ability to perform multivariate analyses and to assess and control for confounding and

interaction. It is possible that reporting for some data may have been influenced by results, eg, HBeAg-positive results may have been more likely to be reported than HBeAg-negative results due to public health laboratory reporting requirements, thereby overestimating the prevalence of HBeAg positivity. Finally, because the unit of analysis focused on mother-infant pairs, maternal characteristics of women giving birth to >1 infant would have contributed disproportionately to the results.

CONCLUSIONS

Timely infant immunoprophylaxis and completion of the 3-dose series prevents most perinatal transmission of HBV and HBV-related morbidity and mortality, as demonstrated by the case management outcomes of infants born to HBsAg-positive pregnant women reported by the EPHBPP. Our results underscore the importance of completing the entire ACIP-recommended immunoprophylaxis regimen, including 4 HepB vaccine doses for infants with birth weights <2000 g born to HBsAg-positive women. Most infants born to HBsAg-positive women who are case managed by the EPHBPP and who receive postvaccination serologic testing do not develop perinatal HBV infection. Our results reaffirm the efficacy of the ACIP recommendations for postexposure prophylaxis as case managed by PHBPP coordinators. Our results also highlight a subset of infants born to younger mothers or Asian/Pacific Islander mothers, or mothers who are HBeAg-positive or who have high viral loads, who still acquire perinatal HBV infection. The identification of women with a higher risk of perinatal HBV transmission in the context of optimal postexposure prophylaxis suggests that interventions such as maternal antiviral therapy might further decrease or eliminate perinatal HBV infections.

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