HHS Public Access

Author manuscript

Am J Obstet Gynecol. Author manuscript; available in PMC 2016 March 01.

Published in final edited form as:

Am J Obstet Gynecol. 2015 March ; 212(3): 365.e1–365.e7. doi:10.1016/j.ajog.2014.09.032.

Postpartum care for mothers diagnosed with hepatitis B during pregnancy

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Abstract

Objective—To determine rates of maternal postpartum hepatitis B virus (HBV) follow-up with a HBV specialist and identify factors associated with poor follow-up, as prior research has focused on infant outcomes and not maternal care.

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Disclosures: CU is an employee of Novartis. The remaining authors report no conflicts of interest.

Study Design—We conducted a retrospective review of data from Partner's HealthCare system, the largest health care system in Massachusetts, and identified women with chronic HBV who delivered from 2002 to 2012.

Results—We identified 291 women (mean age 31.5 years, 51% Asian) with incident HBV during pregnancy. Forty seven percent had postpartum follow-up with a HBV specialist, but only 19% also had appropriate laboratory tests (e antigen [HBeAg], e antibody [HBeAb], HBV DNA, and ALT) checked within 1 year of their HBV diagnosis. Mothers with HBV follow-up were more likely to have a primary care physician (PCP) within the Partners system (66% versus 38%, p<0.0001), a positive HBeAg (20% versus 8%, p=0.004), and elevated AST values (17% versus 8%, p=0.02). On multivariable logistic regression analysis, a mother who had a PCP (OR 2.50 [95% CI: 1.37–4.59]) or positive HBeAg (OR 4.45 [95% CI: 1.64–12.06]) had a greater likelihood of having HBV follow-up.

Conclusion—Only 19% of HBV infected mothers met care guidelines 1 year after being diagnosed with HBV. Inadequate postpartum HBV care affects women of all races/ethnicities. Women who had a PCP as well as those who were HBeAg positive were more likely to be referred for postpartum follow-up with a HBV specialist, suggesting that providers might be referring patients when they perceive HBV to be more serious or complex.

Keywords

adherence; compliance; guidelines; prophylaxis

Introduction

Chronic hepatitis B virus (HBV) infection affects an estimated 2.2 million people in the United States (U.S.) and 350 million people globally, resulting in approximately 1 million deaths annually worldwide from decompensated cirrhosis and hepatocellular carcinoma (HCC).[1, 2] Prophylaxis to prevent vertical transmission from mothers to infants is highly effective and critical to controlling the spread of chronic HBV infection.[3] Thus, screening pregnant women for active HBV infection is standard of care and applied almost universally throughout the U.S. Although mothers are also subject to future risk from untreated HBV, little research has focused on maternal postpartum care and outcomes following prenatal diagnosis of HBV.

According to the American Congress of Obstetrics and Gynecology (ACOG) and American Association for the Study of Liver Diseases (AASLD), appropriate HBV care includes referral to a physician experienced in the management of chronic liver disease, typically a gastroenterologist/hepatologist or infectious disease specialist, for routine liver disease monitoring and HCC surveillance.[4, 5] However, our recent study of a single New York City medical center found that less than 10% of mothers with a positive hepatitis B surface antigen (HBsAg) test during pregnancy received appropriate HBV care postpartum.[6] These mothers and their close contacts are at risk for developing future complications of HBV, including cirrhosis and HCC, which can be prevented by existing antiviral therapies.[7, 8] To further highlight this concern, one mother from our cohort died from metastatic HCC shortly after delivering a healthy infant. Postpartum HBV care is essential not only for maternal

health, but also as a public health measure to prevent HBV transmission to subsequent children as well as close contacts through HBV screening and immunization.[4, 5, 9, 10]

Our prior study was limited to a single New York City medical center with a predominantly Hispanic population and may not be generalizable to other patient populations, and we are unaware of other research addressing postpartum care for HBV. In the current study, we sought to determine rates of postpartum HBV specialty clinic follow-up and identify factors associated with poor follow-up in the Partners HealthCare (Partners) system, the largest health care system in Massachusetts. We hypothesized that poor HBV follow-up would be a prevalent problem among all women.

Materials and Methods

We conducted a retrospective chart review of data from the Partner's HealthCare system, a not-for-profit, integrated health care system, which is comprised of several hospitals, community health centers, numerous other health related services, and >60,000 employees.[11] The two founding institutions, Brigham and Women's Hospital (BWH) and Massachusetts General Hospital (MGH), serve as major teaching affiliates for Harvard Medical School, and perform most of the deliveries at Partners, approximately 8,000 and 3,500 deliveries a year, respectively, accounting for approximately 40% of all deliveries in Boston.[12, 13]

We identified women who delivered at one of two Partners-affiliated hospitals, BWH or MGH, from 2002 to 2012 using the Partners Research Patient Data Registry (RPDR), a centralized electronic data repository of >4 million patients that includes >1 billion diagnoses, medications, laboratory results, procedures, demographic and visit entries. Pregnancy and delivery status was identified using International Classification of Diseases, Ninth Revision (ICD-9) and Diagnosis Related Group (DRG) delivery codes. We then searched for evidence of active HBV infection, which we defined as the presence of a HBsAg+ laboratory test. We included in our analysis women in whom active HBV infection was confirmed by either two positive tests for HBsAg at least 6 months apart, or a single HBsAg+ in conjunction with a negative core IgM, which is in agreement with AASLD and the Centers for Disease Control and Prevention (CDC) definitions of HBV.[4, 14] In rare cases we used clinician judgment to determine whether the patient had HBV infection, such as in the case of a suspected S gene escape mutant. We excluded patients who had established HBV specialty care prior to their first pregnancy within the dataset (index pregnancy).

For the included women, we obtained from the RPDR information on sociodemographic characteristics including age race/ethnicity, marital status, insurance type (commercial compared to non-commerical, including Medicaid, Medicare, subsidized insurance, self-pay, and safety net coverage), and English as the primary language. We also collected information on clinical characteristics that might be associated with postpartum follow-up rates, which included comorbidities (co-infection with hepatitis C virus [HCV], human immunodeficiency virus [HIV]), viral hepatitis serologies, and laboratory indicators that might indicate active liver disease (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin, international normalized ratio [INR], creatinine,

platelet count, albumin, hemoglobin, alpha-fetoprotein [AFP]). When available, postpartum liver biopsy, laboratory, and imaging results were collected. The primary outcome was first time referral for postpartum HBV follow-up with either a gastroenterology/hepatology or infectious disease specialist during which HBV management was addressed in the outpatient provider note.

In bivariate analyses, to compare differences between patients with and without postpartum HBV follow-up, we used the t-test for continuous characteristics, such as for age and most laboratory data, including total bilirubin, INR, creatinine, platelets, albumin, and hemoglobin. We used chi-squared or Fisher's exact test for categorical data, such as race/ethnicity, marital status, insurance type, English as the primary language, presence of comorbidities (HCV, HIV), and for certain laboratory data that we converted into categories, such as elevated ALT. We used characteristics that were found to be significant on bivariate analyses ($p<0.05$) that might affect referral practices and clinically relevant demographics selected a priori, which included race/ethnicity, commercial insurance status, and English as self-reported primary language, in a multivariable logistic regression model to identify independent predictors of postpartum care, reported as odds ratios (OR) and 95% confidence intervals (CI). We conducted all statistical analyses using SPSS Statistics version 21 (Armonk, NY: IBM Corp.).

This project was reviewed and approved by the Partners HealthCare IRB.

Results

From 2002 to 2012, a total of 339 women with chronic HBV delivered at Partners. Fourteen percent (48/339) had documented HBV specialty follow-up before their index pregnancy and so were excluded from the analysis, resulting in a total study population of 291 mothers, among whom we had longitudinal data for median follow-up of 3.3 years (interquartile range [IQR] 6.8). Fifty one percent were Asian and the mean age was 31.5 (standard deviation [SD] 5.6 years). Most women (69%) had only one pregnancy during the study period. A majority indicated English as their primary language (76%) and carried some form of commercial health insurance (54%). Fifty-four percent of mothers were e antibody positive (HBeAb). Forty-four percent (127/291) had all of the laboratory tests recommended by AASLD for HBV management,[4] including HBeAg, HBeAb, HBV DNA, and ALT; of which, 39% (50/127) were chronic inactive carriers, characterized by HBeAg-/HBeAb+ low (<2,000 IU/mL) or undetectable HBV DNA levels and normal ALT. The interval from the time of the initial HBsAg+ until follow-up laboratory testing varied according to type of test checked: ALT a median of 2.1 (IQR 6.5) weeks, HBeAg had a median delay of 3.3 (IQR 13.4) weeks, and HBV DNA a median of 8.1 (IQR 131.3) weeks. One mother was co-infected with HIV and none had HCV. Only 71% of women underwent HIV testing despite recommendations supporting universal screening during pregnancy by the CDC and ACOG in 2006.[15, 16] Women who delivered on or before the 2006 recommendations had a greater proportion of missing HIV tests when compared to women who delivered after (38% versus 16%, respectively, $p<0.0001$). None of the patients had evidence for development of HCC and none died within the study period.

Forty seven percent (137/291) of mothers had postpartum HBV specialty care, 39% (53/137) of whom were seen during pregnancy. The vast majority (95%) were seen by a gastroenterologist/hepatologist, while the rest were seen by an infectious disease specialist. When comparing women with and without postpartum HBV follow-up (Table 1), mothers with HBV follow-up were almost twice as likely to have a primary care physician (PCP) within the Partners system (66% versus 38%, p<0.0001) and, as expected, more likely to have appropriate adjunctive laboratory testing performed including hepatitis A virus (HAV) antibody, HBV e antigen (HBeAg), HBeAb, DNA level, and HCV antibody. A larger proportion of mothers with HBV follow-up were HBeAg+ (20% versus 8%, p=0.004) and had elevated AST values (17% versus 8%, p=0.02). While there was no difference in median DNA levels between groups during the index pregnancy, mothers who had HBV follow-up had higher median peak DNA levels with continued monitoring (5320 international units [IU] [IQR 114,746] versus 305 IU [IQR 2971], p=0.002). Mothers with follow-up were more likely to have an HIV antibody checked and a slightly lower mean creatinine, but the difference was not clinically relevant. Other laboratory results (hemoglobin, platelet count, total bilirubin, albumin, INR) were not different between groups (data not shown).

On multivariable logistic regression analysis, whether a mother had a PCP in the Partners system (OR 2.50 [95% CI: 1.37–4.59], p=0.003) or a positive HBeAg (OR 4.45 [95% CI: 1.64–12.06], p=0.003) (Table 2) each predicted a greater likelihood of having postpartum specialist follow-up. Other characteristics including race/ethnicity, English as self-reported primary language, commercial insurance status, and elevated AST were not independent predictors of follow-up.

There was a median delay of 12.0 months (IQR 59.3) from the time of HBV diagnosis until postpartum HBV specialist follow-up. Although 47% of mothers had HBV specialist follow-up, only 19% (55/291) also had appropriate monitoring with AASLD-recommended laboratory tests evaluated within 1 year of the initial positive HBsAg, which includes HBeAg, HBeAb, HBV DNA, and ALT. Amongst mothers with HBV follow-up, adherence to yearly monitoring was low, ranging from 20–44% depending on the parameter being measured (Table 3). Most mothers had mild HBV disease; 79% had never been treated with antiviral therapy (which consisted of lamivudine, entecavir, tenofovir, or interferon) and only 4 of 22 who underwent liver biopsy had moderate to severe fibrosis (equivalent Ishak 3/6 or more) with only one biopsy that showed cirrhosis. Inflammation was mostly mild.

Comment

In this study of postpartum maternal HBV outcomes in the largest health care system in Massachusetts, we found that less than half of the mothers who were diagnosed with chronic hepatitis B during pregnancy had postpartum follow-up care for their HBV infection and only 19% had recommended laboratory testing within 1 year of their HBV diagnosis. Mothers who had a PCP within the health care system and a positive HBeAg were more likely to have postpartum HBV follow-up. Demographic characteristics, including insurance type and primary language, were not important predictors of follow-up care.

It is unclear why so few women had postpartum HBV care. The low prevalence of HBV in MA may have contributed to patient and provider (obstetrician and PCP) inexperience regarding HBV, although inadequate HBV knowledge and care have also been reported nationwide[17] and in higher prevalence areas.[18–20] Even when seen by a HBV specialist, providers are poorly adherent to AASLD HBV management guidelines, [21] suggesting a multifactorial etiology for this care discrepancy. It is possible that the involvement of a PCP in a patient's care could help facilitate a referral to a HBV specialist; alternatively, having a PCP may merely be a general indicator of a patient's attendance at and adherence to medical care and may not actually reflect the PCP's coordination of care. The greater proportion of HBeAg+ mothers referred for HBV specialty follow-up suggests that providers, obstetricians and PCPs, might be referring patients for what they perceive to be more serious or complex HBV. Factors that often impact access to care, such as race/ethnicity, lack of English language fluency, and commercial health insurance status, did not affect postpartum follow-up. In Massachusetts, the influence of insurance type may have been dampened by the health care reform law of 2006, which provided health insurance for nearly all of its residents.[22] Although disparities in access to care clearly still exist in Massachusetts,[23] there is indirect evidence that health care reform has generally improved access as studies have reported improvements in health outcomes and utilization,[24] and reductions in all-cause mortality.[25] Additionally, we may not have had sufficient power to detect small differences between commercial and non-commercial insurance as overall postpartum HBV follow-up was low in our cohort.

Mothers in our cohort had a mean age of 31.5 years at the time of the index pregnancy for our study, which is higher than the mean 27.7 years that mothers in Massachusetts are during their first birth.[26] This might be explained in part by the mothers in our cohort who had already been pregnant prior to the study period as we did not capture the first pregnancy but the first pregnancy within our study period. Most mothers had mild liver disease without HCV or HIV co-infection and a sizeable proportion (39%) were chronic inactive HBV carriers. Despite the moniker "inactive," chronic inactive carriers are still at risk for developing future complications, namely cirrhosis and HCC. These patients require lifelong surveillance by a physician experienced in the management of chronic liver disease as early antiviral therapy can prevent the progression of liver disease and HCC, [1, 4, 7] and has been shown to be cost effective in decision analysis models.[27] In one study, the risk of developing cirrhosis amongst chronic inactive carriers was 15% over 25 years.[28] It is important to also note that more than half (54%) of the mothers in our cohort who were tested were HBeAb positive and therefore are at risk for developing active hepatitis in the form of HBeAb positive/HBeAg negative chronic hepatitis.

Incidentally, we found that only 71% of women had HIV testing in our system despite recommendations for universal HIV screening during pregnancy by the CDC and ACOG.[15, 16] There are a number of potential explanations for this low HIV testing rate. In our cohort, we found that HIV testing rates prior to the 2006 guidelines were lower than when compared to after, which likely reflects temporal trends in physician practices. Specifically in Massachusetts, HIV testing prior to 2012 required written consent,[29] which further hampered universal testing efforts. When compared to the rest of the state, our HIV testing rates were very similar; according to the Massachusetts Pregnancy Assessment

Monitoring Survey (PRAMS) 2009/2010 Surveillance Report, a collaborative surveillance project between the CDC and the Massachusetts Department of Public Health, only 75.7% of pregnant women were offered an HIV test and even fewer (65.3%) report being tested.[30] A discussion of the various reasons for incomplete HIV testing during pregnancy is beyond the scope of our current study.

We found that mothers experienced median delays of 2.1–8.1 weeks from the time of HBV diagnosis until undergoing recommended HBV laboratory testing, such as HBeAg, ALT, and DNA levels, which are essential for risk stratification to identify women who are highly viremic and might be candidates for antiviral therapy to prevent vertical transmission. Also, obstetrical providers and patients within a large area of New England commonly utilize obstetricians and Maternal-Fetal Medicine specialists at BWH and MGH for prenatal and hospital care of complicated pregnancies, including those associated with advanced maternal age. Specifically, testing for HBeAg and DNA during pregnancy has been shown to be cost effective for reducing perinatal HBV transmission using a Markov decision model.[31] For mothers without HBV specialist follow-up, these laboratory tests were ordered by their obstetrician, PCP, or other medical provider. However, this interval was not shorter amongst mothers who did have HBV specialist follow-up care, although this may be due to the 1 year median delay before being seen by a HBV specialist.

Once under the care of a HBV specialist, mothers were more likely to have a complete laboratory evaluation, which included HAV, HBV, and HCV serologies. However, even amongst those who saw a specialist, adherence to recommended laboratory surveillance with annual ALT and HBV DNA was low, at 21% and 44% respectively. Expert consensus guidelines[4] recommend that these tests should be conducted twice yearly. Routine HCC screening with abdominal imaging, with or without AFP was rare (25%), but this was expected as childbearing women are not the target population for HCC screening according to AASLD guidelines, with the exception of African women who should be screened when older than 20 years. Of note, it was difficult to reliably differentiate recent African immigrants from African Americans, who are not recommended to receive HCC screening, in a retrospective fashion. Additionally, amongst mothers with HBV follow-up, a sizeable proportion (21%) was treated with antiviral therapy at some point peri- or postpartum. It is possible that amongst mothers without HBV follow-up more women might have qualified for treatment, but were never offered the opportunity. This is further illustrated by the fact that, during the index pregnancy, mothers with HBV follow-up had similar initial HBV DNA levels to mothers without HBV follow-up, but with continued follow-up later developed higher peak DNA levels.

Our study was retrospective in nature and limited to a single health system. As a result, our study was unable to pinpoint potential barriers for poor postpartum follow-up, including issues related to patients (nonadherence to appointments), providers (obstetricians not referring patient, or HBV specialists not meeting AASLD guidelines) or systems (challenges in obtaining HBV specialist appointments). We may have underestimated both the burden of HBV disease in our patient population and the rates of appropriate laboratory workup because some prenatal providers, including those of patients transferred to our tertiary care facilities, may utilize laboratories outside of Partners. However, it is likely that most

providers utilizing Partners laboratories for HBV screening will also use these laboratories for additional testing. We also could not identify which provider (obstetrician, PCP, or HBV specialist) was ordering HBV laboratory tests. Both of the delivery hospitals, BWH and MGH, are academic institutions where HBV care is provided by specialists and not PCPs, which may limit the generalizability of our findings in non-academic settings. It is unclear how applicable our findings are to regions of the country with higher HBV prevalence, 10–15% amongst at risk groups, due to larger proportions of immigrants from Asia and Africa, such as in Atlanta, Chicago, New York City, Philadelphia, and California[32, 33] where there is likely to be greater general awareness of HBV amongst patients and physicians. Nevertheless, even in high HBV prevalence areas PCPs are often unfamiliar with HBV guidelines.[34]

In summary, we found that less than half of the mothers who delivered at a large academically-affiliated health system in Massachusetts had follow-up with a HBV specialist postpartum and only 19% met recommended HBV care guidelines 1 year being diagnosed with chronic HBV. Our study was the first to evaluate postpartum HBV follow-up care in a large health care system setting and confirmed that most mothers were not receiving appropriate postpartum HBV care. While HBV is more prevalent amongst Asian and African mothers, inadequate postpartum HBV care affected women of all races/ethnicities, regardless of English as a primary language or commercial insurance status. Having a PCP and HBeAg+, a marker of more aggressive HBV, were associated with postpartum HBV specialty follow-up. This finding suggests that non-patient factors, such as obstetrician knowledge of HBV, may play an important role in adherence to postpartum HBV follow-up care. Future studies are needed to confirm our findings in other health care settings and to evaluate physician, and system-related factors affecting postpartum follow-up care.

Acknowledgments

Funding for EO: K24 HD069408

This study was funded in part by a Partners HealthCare Patient Care Quality & Safety Center of Expertise Research Grant and a Biomedical Research Institute and the Brigham and Women's Hospital Center for Faculty Development and Diversity's Office for Research Careers Microgrant who had no involvement in any aspect of the study or manuscript.

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Table 1

Characteristics of women with chronic hepatitis B (HBV) infection identified during pregnancy, according to postpartum follow-up

Characteristic	Without HBV Follow-Up n=154	With HBV Follow-Up n=137	P value
	Mean (SD), Median (IQR), or N (%)		
Background data			
Mean age, years	31.8 (5.3)	31.2 (6.0)	0.44
Race/Ethnicity			0.59
White	22/154 (14%)	16/137 (12%)	
Asian	73/154 (47%)	76/137 (55%)	
Black	46/154 (30%)	32/137 (23%)	
Hispanic	7/154 (5%)	7/137 (5%)	
Other	2/154 (1%)	3/137 (2%)	
English as self-reported primary language	118/154 (77%)	102/137 (74%)	0.58
Not married	40/154 (26%)	42/137 (31%)	0.43
Commercial health insurance	83/154 (54%)	75/137 (55%)	0.91
>1 pregnancy during study period	47/154 (31%)	42/137 (31%)	1.00
Cesarean section at any pregnancy	41/154 (27%)	44/137 (32%)	0.37
Primary care physician within Partners	58/154 (38%)	90/137 (66%)	<0.0001
Time from initial HBsAg+ until follow-up HBV-related laboratory testing, in median weeks			
HBeAg	3.3 (14.6)	3.3 (11.5)	0.66
HBV DNA	9.7 (146.4)	7.4 (123.0)	0.81
ALT	1.9 (7)	2.4 (6.4)	0.85
Hepatitis laboratory data during and after pregnancy			
Hepatitis A virus (HAV) labs			
Total antibody checked	49/154 (32%)	85/137 (62%)	<0.001
HAV antibody positive†	36/49 (73%)	67/85 (79%)	0.53
HBV labs			
HBc IgM checked†	54/154 (35%)	61/137 (45%)	0.12
HBeAg checked	113/154 (73%)	129/137 (94%)	<0.0001
HBeAg positive	9/113 (8%)	28/129 (22%)	0.004
HBeAb checked	79/154 (51%)	108/137 (79)	<0.0001
HBeAb positive	70/79 (89%)	88/108 (81%)	0.22
DNA checked	63/154 (41%)	114/137 (83%)	<0.0001
Median initial DNA level	413 (3980)	1420 (37960)	0.054
Median peak DNA level ≠	643 (4200)	5320 (114746)	0.002
HBV chronic inactive carrier status	19/38 (50%)	31/89 (35%)	0.118
HCV antibody checked†	100/154 (65%)	119/137 (87%)	<0.0001
HIV antibody checked	102/154 (66%)	106 /137 (77%)	0.04
HIV positive	1/96 (1%)	0/106 (0%)	

Characteristic	Without HBV Follow-Up n=154	With HBV Follow-Up n=137	P value
	Mean (SD), Median (IQR), or N (%)		
Laboratory data during index pregnancy			
Liver enzymes			
ALT checked	134/154 (87%)	121/137 (88%)	0.86
Elevated ALT	15/134 (11%)	22/121 (18%)	0.15
AST checked	133/154 (86%)	121/137 (88%)	0.73
Elevated AST	10/133 (8%)	21/121 (17%)	0.02

† All women were HAV IgM, HBc IgM, and HCV antibody negative

≠ Peak DNA value at any time, including outside of index pregnancy

Table 2

Logistic regression model with HBV specialist follow-up as the outcome.

	Adjusted Odds Ratio (95% CI)
Primary care physician within Partners	2.50 (1.37–4.59)
Race/Ethnicity	
White	1.0 (Ref)
Asian	1.49 (0.59–3.77)
Black	1.39 (0.52–3.74)
Hispanic	1.35 (0.30–6.01)
Other	2.82 (0.22–37.13)
English as self-reported primary language	0.89 (0.43–1.84)
Commercial health insurance	1.21 (0.66–2.24)
HBeAg positive	4.45 (1.64–12.06)
Elevated AST	1.06 (0.40–2.78)

Table 3

Postpartum clinical and laboratory results among mothers with HBV follow-up after delivery

Variable	N=137
Time from HBV diagnosis to HBV follow-up, median months (IQR)	12.0 (59.3)
Yearly adherence, n (%)	
ALT monitoring	60 (44%)
HBV DNA monitoring	29 (21%)
HCC screening	
AFP	27 (20%)
Abdominal imaging	34 (25%)
Antiviral therapy at any time, n (%)	29 (21%)
Tenofovir	17/29 (59%)
Entecavir	7/29 (24%)
Lamivudine	4/29 (14%)
Interferon	1/29 (3%)