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Incidence, determinants and outcomes of pregnancy-associated hepatitis B flares: A regional hospital-based cohort study

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Abstract

Background & Aims: There is limited knowledge about hepatitis B virus (HBV) flare among pregnant women. We evaluated the incidence, determinants and outcomes of HBV flare in a multicultural cohort of pregnant HBV-infected women in the United States.

Methods: We performed a retrospective cohort study of pregnant hepatitis B surface antigen-positive women cared for at hospital-based clinics of 4 medical centres in Southeastern Pennsylvania from 2006 to 2015. The main outcome was incident HBV flare (alanine aminotransferase [ALT] ≥2 times upper limit of normal) during pregnancy or within 6 months after delivery. Among patients with flare, we determined development of jaundice (total bilirubin ≥2.5 mg/dL) and hepatic decompensation. Multivariable logistic regression was used to estimate odds ratios (ORs) of HBV flare for risk factors of interest, including timing of flare (during pregnancy versus post-delivery), nulliparity, younger age, HBV e antigen (HBeAg) status, and lack of anti-HBV therapy.

Results: Among 310 pregnant predominantly African HBV-infected women with 388 pregnancies, the incidence of HBV flare was 14% (95% CI, 10-18%) during pregnancy and 16% (95% CI, 11-24%) post-delivery. Jaundice developed in 12% and hepatic

Abbreviations: ALT, alanine aminotransferase; CI, confidence interval; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IPW, inverse probability weighting; IQR, interquartile range; OR, odds ratio; ULN, upper limit of normal.

decompensation in 2%. Positive HBeAg was associated with HBV flare (OR, 2.55; 95% CI, 1.04-6.20). HBV DNA was measured in 55% of patients, and only 50% were referred for HBV specialty care.

Conclusions: Pregnancy-associated hepatitis B flare occurred in 14% during pregnancy and 16% post-delivery and rarely led to hepatic decompensation. Positive HBeAg was the main risk factor identified. Women did not have adequate HBV monitoring or follow-up during pregnancy.

KEYWORDS

flare, hepatic decompensation, hepatitis B virus, pregnancy

1 | INTRODUCTION

The prevalence of chronic hepatitis B virus (HBV) infection in the United States (US) is rising, largely due to immigration from endemic regions.[1] An estimated 2 million individuals are chronically infected in this country.[2,3] A growing number of chronic HBV-infected women give birth each year in the USA,[4] with more than 25 000 live births annually.[5] Given the goal of elimination of chronic HBV infection,[6] there has been a focus on decreasing mother-to-child transmission of HBV with the implementation of universal infant vaccination, hepatitis B immune globulin administration to newborns of HBV-infected women, and recently updated guidelines outlining indications for antiviral treatment of HBV infection during pregnancy.[7] However, despite this focus on eliminating HBV mother-to-child transmission, there remains limited knowledge on the course of chronic HBV infection among pregnant women.

Observational studies have described significant increases in liver aminotransferase levels in up to 50% of pregnant chronic HBV-infected women, predominantly in the post-partum period within the first 6 months after delivery.[8–11] These HBV flares might be related to immunologic changes that occur during pregnancy and could lead to liver dysfunction, hepatic decompensation or maternal death.[12] However, existing studies have been limited by small sample sizes, inclusion of predominantly Asian patients, evaluation primarily during the post-partum period, and examination of few potential risk factors for HBV flare. Consequently, the epidemiology of HBV flare among HBV-infected pregnant women in the USA remains unknown. These data are important to determine the clinical relevance of HBV flare among chronically infected pregnant women and can inform the need for monitoring of liver-related laboratory tests during and after pregnancy. If HBV flares are predominantly subclinical elevations in liver aminotransferases that resolve spontaneously, close monitoring for these events in pregnant HBV-infected women during and after pregnancy might be unnecessary. Alternatively, if the incidence of HBV flare is high and associated with significant morbidity, particularly in select patient groups, a targeted approach to monitoring, and potentially initiation of treatment with antiviral therapy, may be warranted.

To address these issues, we evaluated the incidence, determinants and outcomes of HBV flare among a cohort of HBV-infected pregnant women receiving care within hospital-based practices in the Southeastern Pennsylvania region of the USA. We hypothesized that post-delivery period, nulliparity, younger age, positive HBV e antigen (HBeAg) status and absence of anti-HBV therapy use during pregnancy would be important risk factors for HBV flare.

Key points

- Knowledge on the course of chronic HBV infection among pregnant women has been limited.
- This cohort study of pregnant HBV-infected women found that the incidence of HBV flare was 14% during pregnancy and 16% after delivery.
- HBeAg-positive status and younger age were associated with a higher risk of HBV flare.
- HBV monitoring and follow-up during pregnancy and within 6 months after delivery were uncommon in this real-world cohort, highlighting the importance of collaboration between obstetricians and clinicians providing HBV specialty care to improve liver outcomes among chronic HBV-infected pregnant women.

2 | PATIENTS AND METHODS

2.1 | Study design and setting

We performed a retrospective cohort study using data from the Southeastern Pennsylvania Hepatitis B Research Network, which was established to facilitate epidemiologic research in HBV infection.[13] The network affords access to demographic data, medical diagnoses, procedures, laboratory results and clinician progress notes from HBV-infected patients in care within general medical and specialty practices at 4 medical centres in this region (University of Pennsylvania, Thomas Jefferson University, Drexel University and Penn State Hershey Medical Center). Institutional Review Board approval for this study was obtained at each site. As this study was retrospective and collected de-identified patient

data, informed consent was not obtained from patients in this study.

2.2 | Study patients

Patients were included if they had the following: (i) positive HBV surface antigen (HBsAg) during pregnancy, and (ii) diagnosis of pregnancy or delivery between 1 January 2006 and 31 December 2015. All eligible patients at each participating site were included. For patients who had multiple pregnancies/deliveries, each pregnancy/delivery was included as a separate observation.

Follow-up for patients began at the initial visit for pregnancy care. The baseline period was defined as the 12 months prior to this visit. Follow-up continued until a study endpoint, death or 6 months after delivery (the time period during which immune restoration after pregnancy might contribute to HBV flare[8,10,12]).

2.3 | Main study outcomes

The primary outcome was incident HBV flare, defined as an alanine aminotransferase (ALT) ≥2 times the upper limit of normal (ULN) during pregnancy or within 6 months after delivery,[14] based on the established cut-off of normal ALT for females (19 U/L).[15] This definition of HBV flare (≥38 U/L) represents a significant liver aminotransferase threshold in pregnancy.[8,10,11] We also evaluated alternative definitions of HBV flare based on different ALT thresholds reflecting varying severity of liver injury, including ALT ≥ 5 times ULN (95 U/L) and ALT ≥ 10 times ULN (190 U/L). As we evaluated incident events, any patient who had a baseline ALT result above the given HBV flare threshold was excluded from that analysis.

Each patient identified as having an HBV flare had their medical records independently reviewed by 2 clinicians (1 hepatologist and 1 obstetrician) to exclude non-HBV-related aetiologies of acute liver injury, including other causes of viral hepatitis, alcohol abuse, drug-induced liver injury, and liver disease specific to pregnancy, particularly acute fatty liver of pregnancy, HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome, and cholestasis of pregnancy. Any disagreements between the 2 clinicians were arbitrated by a third clinician who was a hepatologist.

As a secondary outcome, among patients who had HBV DNA measured at baseline, we determined occurrence of a 1-log increase in HBV DNA from baseline. Further, among persons with HBV flare, we determined development of jaundice (total bilirubin ≥2.5 mg/dL) without alternative explanation and hepatic decompensation (defined by a physician-recorded diagnosis of ascites, spontaneous bacterial peritonitis, variceal haemorrhage and/or hepatic encephalopathy).

2.4 | Data collection

Baseline demographic and clinical data collected from electronic medical records included the following: age, race, ethnicity, country of origin, body mass index, type of health insurance (Medicaid/Medicare, commercial, uninsured), nulliparity, select comorbidities (ie alcohol dependence/abuse, gestational/non-gestational diabetes mellitus, hypertension, hyperlipidemia, human immunodeficiency virus [HIV] coinfection, hepatitis C virus [HCV] coinfection and hepatitis delta virus coinfection, all defined by clinician-recorded diagnoses), receipt of oral nucleos(t)ide analogue therapy (ie adefovir, emtricitabine, entecavir, lamivudine, telbivudine or tenofovir), HBeAg status, HBV e antibody (anti-HBe) status, HBV DNA, ALT, aspartate aminotransferase (AST), total bilirubin, platelet count and international normalized ratio (INR). All ALT results within the baseline period were collected. We calculated the AST-to-platelet ratio index (APRI) and Fibrosis-4 Index for Liver Fibrosis (FIB-4), which are non-invasive measures of hepatic fibrosis.[16–18] APRI was determined using AST and platelet count: (AST [U/L]/upper limit of normal [considered as 40 U/L])/platelet count (10^9/L)] × 100.[16] An APRI > 2.0 accurately identifies cirrhosis (METAVIR stage F4).[17] FIB-4 was calculated using AST, ALT, platelet count and age as: (age [years] × AST [U/L])/((platelet count [10^9/L]) × (ALT [U/L])$^{1/2}$).[18] FIB-4 scores <1.45 identify no/minimal liver fibrosis, and scores >3.25 indicate advanced hepatic fibrosis/cirrhosis.[18]

Longitudinal data collected after the start of follow-up included all results of: ALT, total bilirubin, platelet count, INR, HBV DNA, HBeAg and anti-HBe. We also recorded initiation of nucleos(t)ide analogue therapy, abdominal ultrasound, referral to HBV specialty care, hepatic decompensation events (based on a recorded diagnosis of ascites, spontaneous bacterial peritonitis, variceal haemorrhage or hepatic encephalopathy) and pregnancy complications (determined by clinician-recorded diagnoses).

2.5 | Statistical analysis

Demographic and clinical characteristics at the time of first pregnancy visit were described using frequencies for categorical data and medians with interquartile ranges (IQR) for continuous variables. Point estimates with 95% confidence intervals (CIs) of the incidence of different definitions of HBV flare were determined, overall, by time period (during pregnancy; within 6 months after delivery), and among patients receiving antiviral therapy prior to pregnancy (to determine the effect of HBV treatment on flare incidence).

Hypothesized risk factors for HBV flare included nulliparity, younger age and positive HBeAg (all of which might be associated with a more pronounced immunologic response to HBV during pregnancy[8,10,12]), 6-month time period after delivery (during which immune restoration after pregnancy might increase risk of HBV flare[8,10,12]), and lack of use of anti-HBV therapy (which might allow higher levels of HBV replication and promote HBV flare in the presence of pregnancy-associated immunosuppression[9]). Multivariable logistic regression was used to determine odds ratios (ORs) and 95% CIs of HBV flare associated with hypothesized risk factors.

As some patients did not have ALT measured during or within 6 months after pregnancy, there was potential for ascertaining biased estimates of HBV flare within these time periods. To minimize any bias

TABLE 1 Baseline patient characteristics

Characteristics	Overall[a] (n = 310)
Demographic data	
Median age (years, IQR)	30 (25-33)
Race (n, %)	
Black[b]	148 (49)
Asian	136 (45)
White	13 (4)
Not Reported	6 (2)
Ethnicity (n, %)	
Hispanic	4 (1)
Non-hispanic	299 (96)
Not Reported	7 (2)
Median body mass index (kg/m^2, IQR)	
At delivery	29 (26-32)
At <20 weeks	25 (22-28)
Health insurance (n, %)	
Medicaid/Medicare	171 (55)
Commercial	95 (31)
Uninsured	41 (13)
Unknown	3 (1)
Median number of pregnancies (IQR)	3 (2-4)
Nulliparous (n, %)	86 (28)
Hepatitis B data	
Initial HBV diagnosis determined (n, %)	152 (49)
AST-to-platelet Ratio Index (n, %)	
>2.0	4 (1)
≤2.0	254 (65)
Data not available to calculate	52 (17)
FIB-4 (n, %)	
>3.25	3 (2)
1.45-3.25	11 (6)
<1.45	182 (93)
Data not available to calculate	114 (37)
HBeAg status (n, %)	
Positive	25 (8)
Negative	103 (33)
Not measured	182 (59)
Prescribed oral nucleos(t)ide analogue prior to pregnancy	18 (6)
Liver-related comorbidities	
Hepatitis delta coinfection (n, %)	6 (2)
HIV coinfection (n, %)	5 (2)
Hepatitis C coinfection (n, %)	5 (2)
Alcohol dependence/abuse (n, %)	3 (1)
Other comorbidities	
Diabetes mellitus (n, %)	
Pregestational	6 (2)
Gestational	28 (9)
Pre-existing hypertension (n, %)	15 (5)
Pre-existing hyperlipidaemia (n, %)	1 (0.3)

AST, aspartate aminotransferase; HBeAg, HBV e antigen; HBV, hepatitis B virus; IQR, interquartile range.

[a]For persons with multiple pregnancies, characteristics for the initial pregnancy are presented.

[b]Of those who reported country of origin, 75 patients were native Africans. See Table S1 for African countries of origin.

introduced by these missing data when determining estimates of the incidence of HBV flare and ORs of flare associated with hypothesized risk factors, in a secondary analysis, we re-analysed our data utilizing the inverse probability weighting (IPW) technique.[19,20] IPW assigns each individual's data a weight inversely proportional to their probability of having an ALT measurement.[20] First, we developed a model for the likelihood of ALT measurement using multivariable logistic regression and including twelve variables collected in our database (Table S1). Based on this model, the probability of ALT measurement for each patient was calculated for each patient's covariate profile. The inverse of this fitted probability was then assigned as the weight (IPW) for each patient. Weighted logistic regression with time period as a covariate (ie during pregnancy or within 6 months post-delivery) was then used to estimate the predicted probabilities of different definitions of HBV flare during pregnancy and within 6 months after delivery. A multivariable weighted logistic regression model was also fit to examine the robustness of associations between hypothesized risk factors and incident HBV flare.

To account for correlations between multiple observations from women with repeat pregnancies, robust standard errors were used. All analyses were conducted using Stata 13.1 (Stata Corporation, College Station, TX, USA).

3 | RESULTS

3.1 | Patient characteristics

We identified 310 HBsAg-positive women who had a total of 388 pregnancies during the study period. The characteristics of these patients at their initial pregnancy are reported in Table 1. Black race was most common (49%), with 57 (18%) reporting that their country of origin was in Africa, representing 16 African countries (Table S2A). The second largest group (45%) was of Asian race, with 16 Asian countries represented (Table S2B). Twenty-eight per cent were nulliparous. Forty-nine per cent had HBV infection initially diagnosed

upon presentation to care for pregnancy, and 8% were HBeAg-positive. Alcohol abuse; HIV, HCV and hepatitis delta coinfection; and advanced hepatic fibrosis/cirrhosis by APRI or FIB-4 were rare. Nineteen patients received oral nucleos(t)ide analogue therapy prior to pregnancy (tenofovir: 14; lamivudine: 3; emtricitabine: 2). Twenty-one patients initiated treatment during pregnancy, including 16 during the first or second trimesters (tenofovir: 14; lamivudine: 2) and 5 during the third trimester (tenofovir: 4; lamivudine: 1).

3.2 | HBV-related care during pregnancy

Hepatitis B virus DNA and serologies were rarely assessed during pregnancy (Table 2). Among all 388 pregnancies, 213 (55%) had HBV DNA measured, 154 (67%) had HBeAg assessed, and 124 (32%) had an INR measured. Thirty-seven patients had an HBV DNA level >200 000 IU/mL during pregnancy, but only 21 (57%) initiated antiviral treatment. An abdominal ultrasound was ordered in 32% of women at baseline or during follow-up, and 46% had the test performed. Only 134 (35%) pregnancies had ALT measured within 6 months post-partum.

Referrals to HBV specialty care occurred during 194 (50%) of the pregnancies, and 144 (74%) referred for specialty care presented to their appointment. The majority of referrals (67%) were to a hepatologist. Ten (7%) of the 144 individuals referred for specialty care initiated oral nucleos(t)ide analogue therapy during pregnancy.

3.3 | Incidence of HBV flare, hepatic decompensation and HBV DNA increase

A total of 15/310 (4.8%) patients had a baseline ALT measured within 12 months prior to presentation for pregnancy care (median baseline ALT, 16 U/L; IQR, 12–36 U/L). Among these 15 patients, 4 had an ALT ≥ 38 U/L.

For the overall sample, the number of times ALT was measured during pregnancy and post-delivery varied, with a median 2 measurements (IQR, 1-2) during pregnancy and a median 1 (IQR, 1-1) measurement after delivery. Among the pregnancies during which ALT was measured, 42/311 (14%; 95% CI, 10-18%) developed HBV flare (ALT ≥2 times ULN) during pregnancy, and 22/134 (16%; 95% CI, 11-24%) had an HBV flare within 6 months after delivery (Table 3). For patients who had an HBV flare, the median number of ALT measurements was 4 (IQR, 2-6). Among patients receiving antiviral therapy prior to pregnancy, 4/19 (21%) developed flare during pregnancy, and 2/13 (15%) developed HBV flare post-delivery.

Among the 42 patients identified as having an HBV flare defined as ALT ≥2 times ULN, 19 (45%) had an HBV DNA > 2000 IU/mL, 10 (24%) had an HBV DNA between 20 IU/mL and 2000 IU/mL, and 13 (31%) did not have HBV DNA measured at baseline, during their pregnancy, or within 6 months after delivery.

Table 3 reports the incidence of HBV flare defined by ALT levels of ≥5 times ULN and ≥10 times ULN during pregnancy and post-delivery. The incidence of HBV flare was ≤5% during these time periods with those ALT thresholds. The characteristics of patients meeting these ALT thresholds are presented in Table S3.

TABLE 2 Adherence to pregnancy-related and general hepatitis B virus (HBV) management guidelines among all pregnancies (n = 388)

Management strategy	Frequency
(a) Pregnancy-related HBV management guidelines	
HBV DNA measured before 28 weeks of pregnancy (n, %)	107/372 (29)
HBV treatment initiated if HBV DNA >200 000 IU/mL (n, %)	15/40 (38)
ALT measured within 6 months post-partum (n, %)	135/388 (35)
Specialist referral (n, %)	192/388 (50)
Hepatology	129/192 (67)
Gastroenterology	56/192 (29)
Infectious diseases	7/192 (3.6)
Patient presented to the specialist appointment (n, %)	144/192 (75)
(b) General HBV management guidelines	
HBV DNA measured (n, %)	213/388 (55)
Maximum HBV DNA level (IU/mL) (n, %)	
<100	79/213 (37)
100–2000	49/213 (23)
2001-200 000	48/213 (23)
>200 000	37/213 (17)
Peak total bilirubin ≥ 1.0 mg/dL (n, %)	12/234 (5)
Peak direct bilirubin ≥ 0.4 mg/dL (n, %)	10/169 (6)
INR measured during observation (n, %)	124/388 (32)
HBeAg checked (n, %)	154/388 (40)
Hepatitis delta antibody measured (n, %)	58/388 (15)
Abdominal ultrasound ordered (n, %)	71/223 (32)
Abdominal ultrasound performed (n, %)	69/150 (46)
Prescribed antiviral therapy (n, %)	40/388 (10)
On therapy prior to pregnancy	19/40 (48)
Initiated therapy prior to third trimester	16/40 (40)
Initiated therapy during third trimester	5/40 (12)

ALT, alanine aminotransferase; HBeAg, HBV e antigen; HBV, hepatitis B virus; INR, international normalized ratio.

Based on the IPW analysis accounting for patients with an unmeasured ALT during pregnancy or within 6 months after delivery, the predicted probability of HBV flare defined by ALT ≥ 2 times ULN was 13% (95% CI, 9-17%) during pregnancy and 14% (95% CI, 7-20%) post-delivery. The predicted probabilities of HBV flare defined by ALT ≥ 5 times ULN and ≥10 times ULN were ≤5% during pregnancy and after delivery in these analyses (Table 3).

Overall, among patients who met any ALT definition of flare, 6/50 (12%) patients developed jaundice (5 pre-delivery; 1 post-partum), and 1 (2%) patient with previously documented cirrhosis developed hepatic decompensation (manifested by ascites) and jaundice in the post-delivery period. These patients had no other pre-existing chronic liver disease to explain their hyperbilirubinemia. The other flares did not have any accompanying clinical event documented. Overall,

TABLE 3 Incidence of hepatitis B virus (HBV) flare during pregnancy and within 6 months after delivery based on specified alanine aminotransferase (ALT) thresholds

Flare definition	No. (%) with HBV flare	Predicted probability of HBV flare based on weighted analysis
During Pregnancy	(n = 311)	
ALT ≥ 2 times ULN	42 (14%; 95% CI, 10-18%)	13% (95% CI, 9-17%)
ALT ≥ 5 times ULN	14 (5%; 95% CI, 2-7%)	5% (95% CI, 2-7%)
ALT ≥ 10 times ULN	5 (2%; 95% CI, 1-4%)	2% (95% CI, 0-4%)
Within 6 months after delivery	(n = 134)	
ALT ≥ 2 times ULN	22 (16%; 95% CI, 11-24%)	14% (95% CI, 7-20%)
ALT ≥ 5 times ULN	7 (5%; 95% CI, 2-10%)	4% (95% CI, 0-8%)
ALT ≥ 10 times ULN	5 (4%; 95% CI, 1-8%)	3% (95% CI, 0-7%)

ALT, alanine aminotransferase; CI, confidence interval; HBV, hepatitis B virus; ULN, upper limit of normal.

TABLE 4 Risk factors for hepatitis B virus (HBV) flare, defined as incident alanine aminotransferase (ALT) level ≥2 times upper limit of normal during pregnancy or within 6 months after delivery

Risk factor	Multivariable OR of HBV flare (95% CI)	Multivariable weighted OR of HBV flare (95% CI)
Age (per 1-year increase)	0.91 (0.85-0.97)	0.94 (0.88-1.00)
Nulliparity	0.73 (0.35-1.53)	0.83 (0.33-2.09)
Positive HBeAg	2.55 (1.04-6.20)	3.83 (1.27-11.60)
Lack of antiviral therapy	0.55 (0.24-1.24)	0.74 (0.28-1.95)
Post-delivery period (vs. during pregnancy)	1.22 (0.73-2.04)	1.10 (0.62-1.96)

CI, confidence interval; HBeAg, HBV e antigen; HBV, hepatitis B virus; OR, odds ratio.

pregnancy complications such as miscarriage and preterm delivery were rare (Table S4).

Of the 115 patients who had HBV DNA measured during pregnancy, 6 (5%) patients demonstrated a 1-log increase in HBV DNA from baseline in the prepartum period. Of the 46 patients who had HBV DNA measured post-partum, 6 (13%) had a 1-log increase in HBV DNA from baseline during the post-partum period.

3.4 | Determinants of HBV flare

In multivariable logistic regression analysis (Table 4), positive HBeAg was a significant risk factor for HBV flare (2.55; 95% CI, 1.04-6.20). Older maternal age (each 1 year increase in age) was associated with a lower risk of flare (OR, 0.91; 95% CI, 0.85-0.97). Post-delivery period, nulliparity and lack of antiviral therapy were not determinants of HBV flare. Similar results were observed with the IPW analysis.

4 | DISCUSSION

We found that HBV flare, defined as ALT ≥2 times ULN, developed in 14% of HBV-infected women during pregnancy and 16% after delivery. Similar results were observed in weighted analyses that accounted for patients with unmeasured ALT levels during pregnancy or within 6 months after delivery. Among patients who developed HBV flare, the incidence of subsequent liver complications was low (jaundice, 12%; hepatic decompensation, 2%). Positive HBeAg and younger maternal age were risk factors for HBV flare. These data suggest that the incidence of HBV flare during or within 6 months after pregnancy is low and characterized primarily by subclinical ALT elevations.

The incidence of HBV flare in our cohort was lower than that found in studies of pregnant HBV-infected women from the Netherlands (45%) and Australia (25%), despite using similar ALT flare thresholds.[8,10] Our disparate findings might be due to differences in our study population, which included a small number of patients receiving antiviral therapy for chronic HBV, a minority of HBeAg-positive patients, and a large number of persons of African origin, which might reflect different disease genotypes and activity in the context of pregnancy. A recent US retrospective cohort study that defined ALT flare using a threshold of 5 times ULN (19 U/L) or ≥3 times baseline (whichever was higher) found the incidence of flare to be 6% during pregnancy and 10% within the first 3 months of delivery.[11] These results are more similar in magnitude to those of our study when we examined a flare threshold of ≥5 times ULN.

We found that HBV flares occurred both during pregnancy and in the post-delivery period, but patients who developed jaundice or hepatic decompensation after HBV flare did so more commonly within 6 months after delivery. These results suggest that although HBV flare can occur during pregnancy, the more clinically significant flares may be more likely to occur after delivery, possibly as a consequence of host-mediated immune restoration.[12]

We identified HBeAg-positivity as an important risk factor for HBV flare. HBeAg-positivity is typically associated with higher HBV

DNA levels which, in turn, may subsequently increase the risk of HBV flare. HBeAg should therefore be measured as part of pregnancy care to potentially identify and target this patient group for closer HBV monitoring. In addition, older age was associated with a lower risk of HBV flare, and for every 5-year increase in age, there was a 30% decrease risk of flare. Thus, HBV flares might be limited to patients with certain factors that affect HBV viral replication and lead to a more pronounced host immunologic response, particularly positive HBeAg status and younger age.

We observed a high incidence of flare among patients receiving antiviral therapy for chronic HBV. We found that 21% of pregnant HBV-infected women on antiviral therapy prior to pregnancy developed HBV flare during their pregnancy and 15% developed flare after delivery. We were unable to determine patients' adherence or persistence to antiviral therapy. It is possible that some of the women might not have been adherent to their antiviral treatment or might have discontinued treatment during pregnancy, which could have contributed to the higher than expected incidence of flare observed among this group. Clinicians should emphasize the importance of adherence to antiviral therapy for chronic HBV throughout pregnancy and after delivery in those prescribed this treatment.

Our study has important clinical implications. Obstetricians should monitor HBV-infected women with liver aminotransferases during pregnancy and in the post-partum period, particularly those who are HBeAg positive. Although alternative aetiologies for ALT elevations during pregnancy should be investigated, we observed that the development of a flare in a pregnant or post-partum HBV-infected woman was typically due to HBV infection. Educating obstetrical providers about the potential for ALT flare in this setting is important to provide appropriate management. Patients and providers should be reassured that liver complications arising from a flare occur very rarely. Finally, the long-term impact of HBV flare on liver fibrosis progression remains unknown. However, HBV flares have been shown to increase risk of progression to cirrhosis in other contexts, even when subclinical.[12] Future studies should determine if pregnancy-related HBV flare accelerates progression of hepatic fibrosis.

This study found that monitoring for HBV-related complications during and within the 6 months after pregnancy was infrequent, and there was poor adherence to HBV management guidelines, particularly with regard to initiation of antiviral therapy. Few patients had HBV DNA, HBV serologies or liver-related laboratory tests performed within the 12-month baseline, during pregnancy or within 6 months after delivery. Liver ultrasound for hepatocellular carcinoma screening was also infrequently performed, though few patients would likely have met current recommendations for screening. Similar findings have been observed in other observational studies.[21–23] This may have been due to clinicians' lack of awareness of guidelines for HBV care in pregnant HBV-infected women. Alternatively, inadequate insurance coverage may have prevented these tests from being performed. Our analysis showed that commercially insured patients were more likely to have their ALT measured (Table S1), possibly because of better access to care. Patients with pre-eclampsia were also more likely to have ALT measured, as pre-eclampsia care typically includes liver function test monitoring and increased contact with clinicians. For a majority of the patients in this cohort, pregnancy was the time of initial diagnosis of HBV infection, representing an important opportunity for establishment of HBV care. Implementing targeted reminders within electronic health records could prompt providers caring for pregnant HBV-infected patients to evaluate important HBV care measures, such as HBV DNA, HBeAg testing, and liver function tests, and to consider specialty referral.

There are several limitations to our study. First, not all of the patients in our cohort had ALT levels measured during pregnancy or after delivery, and of those patients who did have results available, the number of measurements varied. Furthermore, some patients were lost to follow-up after delivery, as pregnant patients can obtain health insurance during pregnancy and within 6 weeks post-partum but could lose this coverage and access to care thereafter. We addressed these limitations by performing secondary analyses using inverse probability weighting, and our results were similar to those of the primary analyses. Second, few patients had HBV DNA measured at baseline, during pregnancy, or within 6 months after delivery, limiting our ability to ascertain incident increases in HBV DNA. Third, we might have missed jaundice or hepatic decompensation events occurring after HBV flare if patients presented to hospitals outside of our network. Fourth, given the retrospective nature of this study, we were unable to assess HBV genotype and precore/core mutations, as these are not routinely assessed during outpatient care in the USA. Few patients had hepatic fibrosis assessment with transient elastography, but we did evaluate APRI and FIB-4 scores. Finally, we collected information on alcohol abuse/dependence, but these data were determined by chart review and may be underreported during pregnancy.[24]

Our study had unique strengths. It included a large sample of pregnant HBV-infected women from diverse sites of care. We evaluated different definitions of HBV flare, characterized by a variety of clinically relevant ALT thresholds. Based on prior studies of HBV flare in the setting of pregnancy,[8,10,11] we utilized the most established cut-off of ALT ≥ 2 times ULN as the primary endpoint. However, alternative ALT thresholds were also examined as secondary outcomes. We reviewed the medical records of each patient who had an HBV flare to rule out non-HBV-related aetiologies. We also determined subsequent development of jaundice, hepatic decompensation and pregnancy complications. Each site had access to HBV specialty care available, allowing us to evaluate referrals for HBV infection and antiviral treatment recommendations. Finally, our statistical analyses accounted for the potential lack of measurement of ALT levels in clinical practice.

5 | CONCLUSION

In this multicultural cohort of pregnant HBV-infected women in the USA, HBV flare developed in 14% during pregnancy and 16% after delivery, and the majority were subclinical in nature. Positive HBeAg and younger age were risk factors for HBV flare. Pregnant HBV-infected

women at high risk of flare should be monitored closely during pregnancy to identify these events as early as possible.

CONFLICT OF INTEREST

Dr. Lewis has served as a member of a Data and Safety Monitoring Board for Gilead for work unrelated to hepatitis B. All other authors report no relevant disclosures.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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