

The characteristics and predictors of postpartum hepatitis flares in women with chronic hepatitis B

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- Introduction:** We aimed to characterize postpartum disease flares among treatment-naïve mothers with chronic hepatitis B (CHB). CHB mothers were enrolled and compared with non-infected mothers in terms of postpartum alanine aminotransferase (ALT) abnormalities.
- Methods:** Demographic, virological, and biochemical parameters were collected up to postpartum week 16, with flares and exacerbations defined as ALT levels 5–10 and >10 times the upper limit of normal, respectively. Outcome assessments included ALT flares or exacerbation and their predictive parameters.
- Results:** Among 4236 patients enrolled, 869 and 3367 had no infection (group A) and had CHB (group B), respectively. Infected mothers were further stratified into two subgroups by the presence (B1, $n=1928$) or absence (B2, $n=1439$) of detectable serum levels of hepatitis B virus (HBV) DNA (lowest level of quantitation, 100 IU/mL). A significantly higher frequency of abnormal ALT levels was observed in group B vs. group A (28.27 vs. 20.37%, $p<0.001$). ALT events mainly occurred in group B1 (flares, 115/1928, 5.96%; exacerbations, 57/1928, 2.96%). The ALT levels had a bimodal pattern, with peaks at postpartum weeks 3–4 and 9–12. On multivariate analysis, elevated ALT levels and detectable levels of HBV DNA at delivery were independent risk factors for postpartum disease flares. Further subgroup analysis in group B1 demonstrated that a cut-off HBV DNA level of 5 log₁₀ IU/mL at delivery predicted ALT events (positive predictive value, 14.4%; negative predictive value, 98.2%).
- Conclusions:** Postpartum ALT level elevation is common in CHB patients. ALT flares or exacerbations are mainly observed in mothers with elevated ALT or HBV DNA levels ≥ 5 log₁₀ IU/mL at delivery.

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INTRODUCTION

The natural history of chronic hepatitis B virus (HBV) infection can be divided into several phases based on viral–host interactions. In the initial phase, after acute infection, some patients may remain positive for hepatitis B virus e antigen (HBeAg), with high levels of serum HBV DNA but with few or no symptoms, normal alanine aminotransferase (ALT) levels, and minimal histological activity in the liver. This is known as the immune tolerance phase, which usually lasts for years in those who acquire the infection during the perinatal period [1]. When the tolerogenic effect is lost during the immune tolerance phase, immune-mediated lysis of infected hepatocytes occurs, along with elevations

in ALT levels. Patients then enter the second stage, defined as the immune clearance phase. This phase may last from months to years. With successful immune control, some patients eventually enter the inactive (carrier) stage, in which sero-conversion of HBeAg to hepatitis B e antibody occurs, HBV DNA becomes non-detectable or remains at low levels, and ALT level is usually normal, reflecting very little or no replication of HBV and mild or non-existent hepatic injury. Patients in this stage can experience spontaneous resolution of hepatitis B and production of hepatitis B surface antibody. However, only a few of these patients undergo spontaneous or immunosuppression-induced reactivation of chronic hepatitis B (CHB), featuring elevated

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ALT levels and high levels of HBV DNA, with or without HBeAg sero-reversion.

In areas where HBV is endemic, the majority of women with CHB who are of childbearing age are in the immune tolerance phase [2]. Although mild-to-moderate elevations of ALT levels during pregnancy have not been clearly linked to pregnancy complications in mothers with CHB [3], a recent study reported that severe ALT flares can cause maternal death [4]. In contrast, few studies have reported on the impact of pregnancy on disease activation or the progression of CHB, especially after delivery [5, 6]. Patients with possible postpartum ALT flares could be divided into three subpopulations: (1) patients with active CHB who are on antiviral therapy during pregnancy and continue on with postpartum treatment (on-treatment flares); (2) patients who are in the immune tolerance phase and treated with antiviral therapy for the prevention of vertical transmission before delivery and therefore discontinue treatment postpartum; and (3) patients who are not on antiviral therapy, both during pregnancy and postpartum, up to the time of ALT flares, with antiviral therapy provided after severe ALT flares. However, on-treatment ALT flares have been reported in many clinical phase III trials. In addition, a recent randomized controlled trial (RCT) on the prevention of maternal-to-child transmission (MTCT) using tenofovir disoproxil fumarate (TDF) reported on the pattern and severity of postpartum ALT flares among immune tolerance mothers who were treated during the antepartum period but discontinued TDF postpartum [7]. Therefore, the current study selected patients who did not receive antiviral treatment during pregnancy and compared their postpartum ALT changes with those of non-HBV infected mothers. The mechanism of ALT flares in these patients has not been fully understood. It has been suggested that rapid changes in the levels of maternal corticosteroids during the postpartum period lead to active immunological responses to HBV [5]. Consequently, intense inflammatory activity may result in hepatic flares or acute necrosis. However, few data exist of postpartum ALT flares for mothers with CHB who did not receive antiviral therapy during the pregnancy [5, 6, 8–10]. Previously published studies have reported conflicting results, not only in terms of the percentage of mothers (10–57%) who experience ALT flares [8, 10] but also regarding factors that can predict ALT flares during the postpartum period [5, 8]. In addition, the clinical features of postpartum ALT flares and clinical outcomes have not been well characterized. With the above in mind, we conducted a large case–control study with consecutive treatment-naïve patients (defined as no antiviral therapy before the ALT flares) over an 8-year period to investigate the changes in ALT levels during the postpartum period, explore the factors associated with these changes, and determine the clinical outcomes of ALT flares.

PATIENTS AND METHODS

Study design and population

We conducted a large case–control study to assess postpartum ALT flares and exacerbations in mothers with CHB at Beijing Ditan Hospital, China. The study site is an infectious disease hospital and serves a large HBV-infected population. Eligible con-

secutive patients were retrospectively enrolled between October 1, 2008, and December 31, 2015. The Institutional Review Board approved the study (approval number: JDL2016 [001]–02), and the need for informed consent was waived. Treatment-naïve patients were assigned into either group A if they had no CHB (controls) or group B if they had CHB (cases). Included in group A were healthy mothers who did not receive therapy during pregnancy and the postpartum period, before the ALT flares, and for whom test results of a liver panel were available within 8 weeks before delivery, at delivery, and during at least one follow-up, with test results available within 16 weeks after delivery. In addition, patients in group A were selected based on the absence of CHB (negative for both hepatitis B surface antigen [HBsAg] and hepatitis B core antibody [HBcAb]). Included in group B were mothers who were treatment-naïve to antiviral therapy and had two positive HBsAg tests before pregnancy, at least 6 months apart. The major exclusion criteria for both groups A and B were coinfection with hepatitis C virus (HCV), hepatitis D virus, or human immunodeficiency virus; autoimmune liver disease; primary biliary cirrhosis; liver cirrhosis; fatty liver diagnosed by sonogram; intrahepatic cholestasis of pregnancy; liver cancer; and alcohol-related liver diseases (consumption of >20 g/day of alcohol for >5 years). Patients with other liver diseases including drug-induced liver injury, thyroid dysfunction, or complications during pregnancy were also excluded. These complications included eclampsia, gestational hypertension, and diabetes.

Data collection and outcome assessment

Using an electronic medical record system and paper charts, the following data from the clinic and inpatient services at Ditan Hospital were collected for analysis: baseline information before delivery including age, history of liver disease, or hepatocellular carcinoma; pregnancy and obstetric complications; pertinent physical findings; and laboratory information including HBV virological markers, chemistry panel results, and imaging results. Data regarding medications, pregnancy complications, and obstetric complications were also collected. Data were assessed at seven time points: 8 and 4 weeks before delivery; at delivery; and at postpartum weeks 4, 8, 12, and 16. Data were allocated to the more recent time point if the tests were performed between two time points. Although clinical parameters at delivery were used as baseline values, data at weeks 4 and 8 before delivery were included in the risk factor analysis of ALT flares.

The primary endpoint of the study was the proportion of mothers with ALT elevation within 16 weeks after delivery, which was compared between the two groups. The secondary endpoints included subgroup analyses of the frequency of ALT elevations in mothers with CHB, which was done by comparing mothers with and without detectable levels of HBV DNA. In addition, we performed subgroup comparisons between mothers who were HBeAg-positive and those who were HBeAg-negative. We analyzed the patterns and amplitudes of ALT flares and compared clinical outcomes after ALT flares or exacerbations, including serological changes and negative clinical events. In addition, we explored the factors associated with elevations in ALT levels in each group and subgroup. An ALT flare was defined as a serum ALT level ≥ 5 times the upper

limit of normal (ULN) up to a maximum of 10 times the ULN (normal ≤ 40 U/L). ALT exacerbation was defined as a serum ALT level >10 times the ULN [10].

Maternal standard of care and laboratory tests

According to the standard of care in our center, pregnant women attended the outpatient clinic for maternal care and were scheduled for routine examinations and laboratory tests every 2–4 weeks during pregnancy and every 4–6 weeks after birth until postpartum week 16. The details of patient histories and physical findings were recorded during visits. Blood tests at each visit, including complete blood count and chemistry with transaminases, were performed at the central laboratory of Ditan Hospital. Viral hepatitis screening was part of the standard of care. HBV serological markers were measured by chemiluminescent micro-particle immunoassay (Architect i2000 analyzer; Abbott Diagnostics, Abbott Park, IL, USA). Serum HBV DNA was tested by real-time quantitative PCR (Piji Co., Ltd, Shenzhen, China) with a detection range of 100–8 \log_{10} IU/mL. ALT level was tested using a Hitachi 7600 fully automatic biochemical analyzer, with the ULN set at 40 U/L (Wako Pure Chemical Industries, Ltd., Osaka, Japan).

Statistical analysis

Descriptive values were expressed as means \pm standard deviations or medians and interquartile ranges (Q1, Q3), depending on the underlying distribution of the data. Student's *t*-test was used to assess continuous variables. Frequencies and percentages were used to summarize categorical variables. Chi-squared test or Kruskal–Wallis test was used to compare these data. Multi-classification logistic regression and receiver operating characteristics analyses were used to investigate factors and their ability to predict ALT flares and exacerbations. The trends in ALT changes after delivery were analyzed using a mixed linear model by repeated measurements with missing value analysis [11]. Data analyses were performed using the Statistical Package for Social Science for Windows, Version 13.0 (SPSS Inc., Chicago, IL, USA). All tests were two-tailed with 95% confidence interval, and statistical significance was set at $p < 0.05$.

RESULTS

Study participants

During the enrollment period, the consecutive medical records of pregnant women who attended postpartum visits at our center were reviewed. Among them, 5813 patients were treatment-naïve with complete clinical data and eligible for screening. We excluded 1577 patients due to presence of HCV and syphilis infection, cirrhosis, postpartum hemorrhage, or other exclusion criteria (Fig. 1). Enrolled patients ($n = 4236$) were classified according to HBV infection status into either group A (non-infected mothers, $n = 869$) or group B (patients with CHB, $n = 3367$). Among those in group B, subgroups were formed if the levels of HBV DNA were detectable (group B1) or undetectable (group B2), based on the lowest level of quantitation (100 IU/mL). All patients in group B2 were HBeAg-negative. In group B1, patients were further assigned

into group B1a if their HBeAg status was positive or group B1b if negative. The patients who were screened and enrolled into the different study groups are shown in Fig. 1. For the entire cohort, the mean age was 29.01 ± 4.21 years, with a mean number of previous pregnancies per patient of 1.90 ± 1.10 . At delivery, the mean number of gestational weeks was 39.21 ± 1.04 , and the median (with interquartile range) ALT and aspartate aminotransferase (AST) levels were 12.60 (9.50–18.28) and 18.00 (15.20–22.80) U/L, respectively. The clinical characteristics of patients at delivery in each group are shown in Table 1. When compared to non-infected patients (group A) or those without detectable levels of HBV DNA (group B2), CHB patients with detectable levels of HBV DNA (group B1) were significantly older; had higher mean values of ALT, AST, and total bilirubin; and a higher frequency of abnormal ALT. However, the numbers of pregnancies or deliveries did not differ among the groups. In patients with detectable levels of HBV DNA (group B1), the mean levels were $5.49 \pm 1.85 \log_{10}$ IU/mL. Furthermore, significantly higher levels of HBV DNA were observed in group B1a when compared to group B1b ($6.53 \pm 1.44 \log_{10}$ vs. $4.27 \pm 1.51 \log_{10}$ IU/mL, $p < 0.001$), which is understandable because we assigned all HBeAg-positive patients to group B1a.

Frequency and severity of ALT flares or exacerbations

During the postpartum follow-up period of 16 weeks, ALT flares and exacerbations occurred in 3.02% (128/4236) and 1.39% (59/4236) of patients in the entire cohort. The majority of these patients was members of group B1 and had detectable levels of HBV DNA. The patients in this group with ALT flares and exacerbations represented 89.84% (115/128) and 96.61% (57/59) of the entire cohort, respectively. In contrast, the aforementioned events occurred rarely in patients without detectable HBV DNA or in non-infected patients. When compared with the non-infected patients (group A), a significantly higher frequency of any ALT abnormality was observed in patients with CHB (group B) [20.37 vs. 28.27%, $p < 0.001$]. ALT flares and exacerbations were present in 3.50% (118/3367) and 1.72% (58/3367) of patients in group B, respectively. The aforementioned events occurred significantly more frequently in group B when compared to the rates of 1.2% (10/869) and 0.1% (1/869) reported in group A (ALT flares, $p < 0.001$; exacerbation, $p < 0.001$). The comparisons of the frequencies of ALT flares and exacerbations among groups are shown in Table 2.

In patients with ALT flares or exacerbations, the reported clinical symptoms were as follows: fatigue, 59; poor appetite, 32; nausea, 12. These patients were all from group B. In contrast, among the 11 patients with ALT flares or exacerbation in the control group (1.3% of the patients in group A), all patients were asymptomatic despite the ALT events. None of the patients in the entire cohort had elevated bilirubin during the aforementioned events. However, 76 patients with ALT flares or exacerbations in group B received antiviral therapy during the first 16 weeks of the postpartum follow-up period. Among them, 27 were prescribed entecavir, 21 adefovir, 8 lamivudine, 5 telbivudine, and 15 pegylated interferon. Serological negativity or sero-conversion for HBeAg or HBsAg did not occur in these patients.

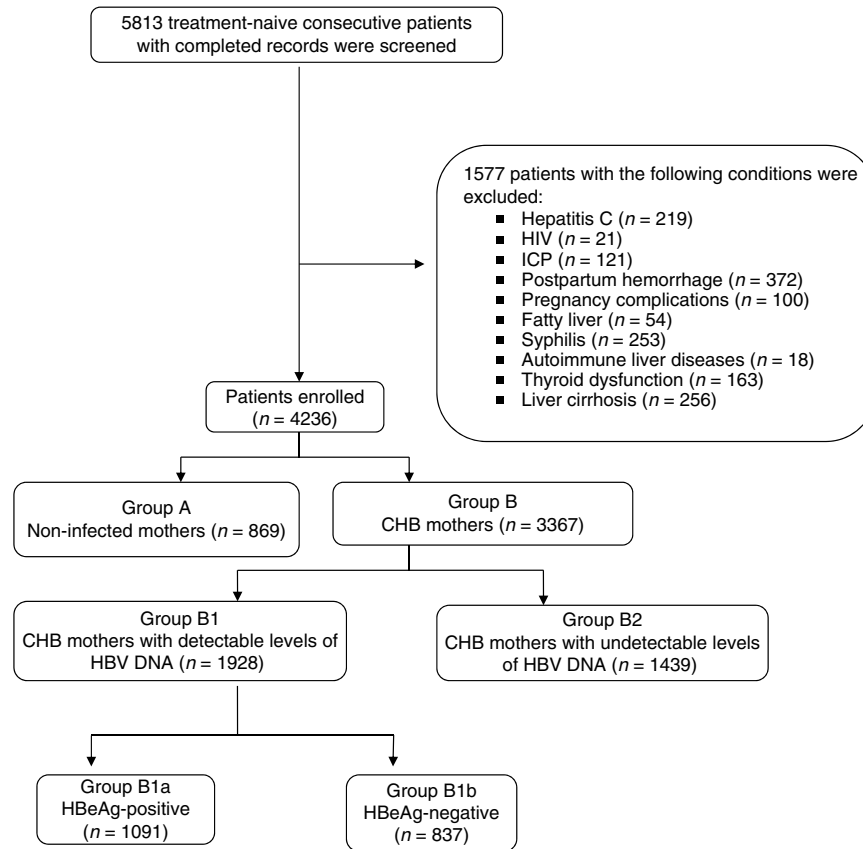


Fig. 1 Flowchart of the study showing the patients enrolled in the study and those who were excluded from the analyses. HIV human immunodeficiency virus, ICP intrahepatic cholestasis of pregnancy, HBV hepatitis B virus, CHB chronic hepatitis B, HBeAg hepatitis B e antigen

Subset analysis stratified by viremia and HBeAg status

Two subset analyses were performed, based on HBV DNA levels and HBeAg status. For the first sub-analysis, patients with detectable levels of HBV DNA were assigned to group B1 ($n = 1928$) and those with undetectable levels to B2 ($n = 1439$). When comparing the two groups, a significantly higher frequency of ALT abnormalities (any degree of elevation) was observed in group B1 (34.96% [674/1928] vs. 19.32% [278/1439], $p < 0.001$). ALT flares were also present in a significantly higher proportion of patients in group B1 (5.96% [115/1928] vs. 0.21 [3/1439], $p < 0.001$). In addition, ALT exacerbations occurred significantly more frequently in group B1 (2.96% [57/1928] vs. 0.07% [1/1439], $p < 0.001$).

In subgroup analyses, the clinical outcomes associated with ALT flares or exacerbations in group B1 were as follows: 58 patients reported fatigue, 32 had poor appetite, and 12 complained of nausea. In contrast, no patients reported symptoms, except one who experienced fatigue during the ALT events, among patients in group B2. As in the data for the entire cohort, there were no patients with elevated bilirubin level during ALT flare or exacerbation events. In addition, no patients experienced serological outcomes of HBeAg negativity or sero-conversion during the observation period if they were HBeAg-positive at baseline. Neither HBsAg status conversion to negative nor sero-conversion occurred in patients with CHB in our study.

The second subgroup analysis was performed according to HBeAg status. Since all patients with undetectable levels of HBV DNA (group B2) were HBeAg-negative and their hepatitis B disease phases differed from those who were HBeAg-negative with viremia (group B1), patients in group B2 were not included in the HBeAg subgroup analysis. In addition, the data for group B2 had been included in the first subgroup analysis. Among the 1928 patients in group B1, the 1091 who were HBeAg-positive were labeled as group B1a and the 837 HBeAg-negative patients as group B1b for comparison and analysis. When comparing the two groups, a significantly higher frequency of ALT abnormalities was observed in group B1a than in group B1b (45.83% [500/1091] vs. 20.79% [174/837], $p = 0.002$). In addition, ALT flares were also observed in a significantly higher proportion of patients in group B1a than in group B1b (9.72% [106/1091] vs. 1.08% [9/837], $p < 0.001$). Finally, ALT exacerbations occurred significantly more frequently in group B1a than in group B1b (4.49% [49/1091] vs. 0.96% [8/837], $p < 0.001$).

Although ALT abnormalities were significantly more frequent and severe in group B1a, the clinical outcomes associated with these events were not severe. None of the patients in the subgroups had an elevated bilirubin level during these events. In group B1a, 56 patients complained of fatigue, 31 patients had poor appetite, and 10 reported nausea. In contrast, among patients who expe-

Table 1 Baseline characteristics of the study group

Values	Group A (n= 869)	Group B (n= 3367)	p-Value (A vs. B)	Group B1 (n= 1928)	Group B2 (n= 1439)	p-Value (B1 vs. B2)
Age (years)	28.46 ± 4.35	29.15 ± 4.16	<0.001	28.90 ± 4.35	29.50 ± 3.85	<0.001
No. of pregnancies	1.96 ± 1.10	1.88 ± 1.09	0.054	1.85 ± 1.073	1.93 ± 1.11	0.018
No. of deliveries	1.19 ± 0.43	1.20 ± 0.44	0.660	1.19 ± 0.429	1.21 ± 0.44	0.313
Gestational weeks	39.20 ± 1.07	39.21 ± 1.03	0.837	39.22 ± 1.05	39.19 ± 1.02	0.646
ALT level (U/L)	10.50 (8.10, 15.20)	13.10 (10.00, 19.20)	0.942	14.80 (11.00, 23.00)	11.50 (8.80, 15.50)	<0.001
ALT abnormal (>40 IU/L)	n=75 (8.63%)	n=287 (8.52%)	0.920	n=226 (11.72%)	n=61 (4.24%)	<0.001
AST level (U/L)	16.90 (14.20, 21.05)	18.30 (15.50, 23.40)	0.858	19.50 (16.30, 25.58)	16.90 (14.60, 20.30)	<0.001
TBil level (µmol/L)	7.30 (6.00, 9.40)	7.60 (6.20, 9.50)	0.550	7.60 (6.20, 9.50)	7.50 (6.20, 9.40)	0.027
ALB level (g/L)	36.10 (33.60, 38.30)	35.50 (33.20, 37.80)	0.016	35.50 (33.00, 37.80)	35.60 (33.30, 37.70)	0.940
HBeAg(+)	—	—	—	1091/1928 (56.59)	0/1439 (0)	—
HBV DNA (log ₁₀ IU/mL)	—	—	—	5.49 ± 1.85	—	—
Group B1a ^a	—	—	—	6.53 ± 1.44	—	—
Group B1b	—	—	—	4.27 ± 1.51	—	—

Values are presented as n (%), means ± standard deviations, or medians (Q1, Q3)
 Group A, non-infected mothers; group B, chronic hepatitis B-infected mothers; group B1, chronic hepatitis B with detectable levels of HBV DNA (left lower quadrant = 100 IU/mL); group B2, chronic hepatitis B with undetectable levels of HBV DNA. Group B2 was further divided into subgroups B1a and B1b based on HBeAg status
 HBeAg hepatitis B surface antigen, HBV hepatitis B virus, HBeAg hepatitis B envelope antigen, ALT alanine aminotransferase, AST aspartate aminotransferase, TBil total bilirubin, ALB albumin
^aGroup B1a vs. group B1b, p < 0.001

Table 2 Frequency of postpartum ALT flares and exacerbations

Cases, n (%)	Total (n= 4236)	Group A (n= 869)	Group B (n= 3367)	p-Value (A vs. B)	Group B1 (n= 1928)	Group B2 (n= 1439)	p-Value (B1 vs. B2)
Normal ALT	2920 (68.93)	681 (78.37)	2239 (66.51) ^a	<0.001	1082 (56.12)	1157 (80.40) ^b	<0.001
Any abnormal ALT	1129 (26.65)	177 (20.37)	952 (28.27) ^c	<0.001	674 (34.96)	278 (19.32) ^d	<0.001
ALT flares	128 (3.02)	10 (1.15)	118 (3.50) ^e	<0.001	115 (5.96)	3 (0.21) ^f	<0.001
ALT exacerbation	59 (1.39)	1 (0.11)	58 (1.72) ^g	<0.001	57 (2.96)	1 (0.07) ^h	<0.001

Values are presented as n (%)

Normal alanine aminotransferase (ALT), <40 U/L; abnormal ALT, ≥40 U/L but <5 times the upper limit of normal (<200 U/L); ALT flare, ≥5 times the upper limit of normal (≥200 U/L) but <10 times the upper limit of normal (<400 U/L); ALT exacerbation, ≥10 times the upper limit of normal (≥400 U/L)

^aChi-squared = 45.426, p < 0.001

^bChi-squared = 218.09, p < 0.001

^cChi-squared = 22.068, p < 0.001

^dChi-squared = 99.381, p < 0.001

^eChi-squared = 13.060, p < 0.001

^fChi-squared = 80.734, p < 0.001

^gChi-squared = 12.996, p < 0.001

^hChi-squared = 40.566, p < 0.001

rienced ALT events in group B1b, two patients complained of fatigue, one had poor appetite, and two reported nausea. Again, none of the patients had changes in their HBeAg or HBsAg status during the study period.

Patterns of ALT flares or exacerbations

To investigate the appropriate frequency and optimal timing of monitoring for postpartum ALT flares or exacerbations, the trends

in ALT changes after delivery were analyzed by compiling the data from all groups and subgroups. A mixed linear model, with repeated measurements and missing values analysis, was used to analyze the trends in ALT changes during the postpartum period [11]. After delivery, median ALT levels were elevated at postpartum week 1 in all the groups. However, the between-group trends differed from those at postpartum week 2 and beyond. In non-infected mothers, ALT level quickly trended down in 2 weeks after

delivery and approached the baseline level at postpartum week 4. The levels then remained stable throughout the remainder of the 16-week observation period. In contrast, mothers with CHB had fluctuating ALT levels, with a bimodal pattern of peak ALT levels observed at postpartum weeks 3–4 and 9–12. Compared with the other groups, HBsAg-positive patients with viremia had the highest median levels of ALT during the peak time points of postpartum elevation. The patterns and amplitudes of ALT changes after delivery in each group are presented in Fig. 2.

Using the aforementioned mixed linear model, the compound symmetry diagonal offset of repeated measures equaled a Z -value of 33.465 with $p < 0.001$, indicating that the hypothesis test of the repeated measurement structure satisfied the requirement and the model was reasonable. The results demonstrated that, among the three selected groups (groups A, B1, and B2), ALT levels at 1 week postpartum were significantly different ($F = 40.874$, $p < 0.001$), and the trends in ALT level changes during the observation period also differed significantly among the three groups ($F = 4.692$, $p = 0.009$). However, there were no significant interactions between baseline ALT levels and trends of ALT changes ($F = 3.432$, $p = 0.064$).

Predictors of ALT flares and exacerbations

To better understand whether baseline values and ALT levels before delivery can predict postpartum ALT flares or exacerbations, we performed multivariate classification logistic regression analysis to compare the maternal baseline variables of mothers with postpartum ALT flares or exacerbations (cases) to those of mothers who did not experience such events (controls). After adjusting for the baseline variables listed in Table 1, two independent predictors were found to be associated with ALT events. First, ALT levels at delivery were independent predictors for both postpartum ALT flares (chi-squared = 204.434, $p < 0.001$) and ALT exacerbations ($Z = 9.397$, Exp [B] = 1.004, $p = 0.002$). Second, HBV DNA levels at delivery were independent predictors for both postpartum ALT flares (chi-squared = 48.439, $p < 0.001$) and ALT exacerbations ($Z = 28.953$, Exp [B] = 2.054, $p < 0.001$).

Further subgroup analyses were performed to study the relationship between HBV DNA and ALT levels in viremic patients in group B1. The subgroups were formed by stratifying patients according to whether their ALT levels were within the normal range (< 40 U/mL) or mildly to moderately elevated (40 to < 200 U/L) or indicated ALT flares (200 to < 400 U/L) or exacerbations (≥ 400 U/L). When data from individual patients were compiled, the mean HBV DNA levels of the aforementioned groups were $5.11 \pm 1.89 \log_{10}$ IU/mL, $5.76 \pm 1.71 \log_{10}$ IU/mL, $6.73 \pm 1.34 \log_{10}$ IU/mL, and $6.96 \pm 1.10 \log_{10}$ IU/mL, respectively. The differences were statistically significant ($F = 52.370$, $p < 0.001$) among the four groups. In addition, HBV DNA levels were the only independent predictors of postpartum ALT elevation, flares, and exacerbations ($F = 15.321$, $p < 0.001$), when adjusting for other baseline factors in group B1. Receiver operating characteristic curves (ROC) analysis was performed for different cut-off points of HBV DNA levels for postpartum ALT flares or exacerbations. Our data indicated that the cut-off value of HBV DNA level for

predicting these ALT events was 5.01 \log_{10} IU/mL with a positive predictive value of 14.4% and negative predictive value of 98.2%. The area under the ROC curve was 0.715 ($p < 0.001$), with a sensitivity of 0.912, specificity of 0.560, and Youden's index of 0.73.

DISCUSSION

Hepatitis B infection has negative impacts on pregnancy outcomes and leads to higher rates of pregnancy-related complications [12]. Hepatitis B flares due to pregnancy have been reported during the antepartum or postpartum periods and are associated with maternal mortality [3, 4, 6]. Rapid changes in immunological status from suppression to activation during the postpartum period are considered as triggers of hepatitis B flares in response to decreasing corticosteroid levels after delivery [5]. Postpartum management of patients who have received antiviral therapy during pregnancy is less challenging because many of them will discontinue treatment if they are still at the immune tolerance phase. The risk of severe post-treatment ALT flares is rare based on a recent RCT of using TDF on preventing MTCT [7]. In other treatment experience, mothers are often at the immune clearance phase or have significant fibrosis, which requires the continuation of therapy during postpartum; thus, ALT flares could be managed as on-treatment flares. However, postpartum hepatitis B flares among mothers who have not received prior antiviral treatment remain a problem because few data exist to guide the management of flare events, and detailed recommendations are not yet included in the major professional guidelines [13,14]. Although five studies focusing on hepatitis B flares in treatment-naïve mothers have been published, they reported conflicting results [5, 6, 8, 10, 15]. In addition, 4 of the 5 aforementioned studies used a retrospective design [6, 8, 10, 15], and 3 enrolled ≤ 40 mothers [6, 10, 15]. One of the most important reasons of inconsistent results may be due to the fact that many of these studies did not classify patients based on HBV DNA, HBsAg status, and HBV disease phases. Therefore, the result of the individual study represented outcomes of a mix patient population of viremic patients and those with undetectable HBV DNA levels, which may lead to different conclusions and conflicting reports among studies. To obtain sufficient power to predict the frequency, severity, and pattern of postpartum ALT flares, we enrolled 4236 patients in the current study. The cohort was well characterized and well defined into subgroups for outcome analyses.

In the present study, maternal demographics were well matched among the groups, although patients were slightly older in the non-HBV-infected group. In previously published studies, the frequency of ALT events has been reported to be 10–57% [5, 6, 8, 10, 15]. Our results indicate that HBV DNA level at delivery was an independent risk factor for ALT flares. Patients with detectable levels of HBV DNA had a 30% chance of flares compared with 20% in those without viremia. The inconsistencies in previously reported results might reflect differences in the composition of the study populations, with patients having different levels of viremia. Moreover, based on previous studies suggesting that the majority of ALT events occur within 12 weeks postpartum [5, 8], we used 16

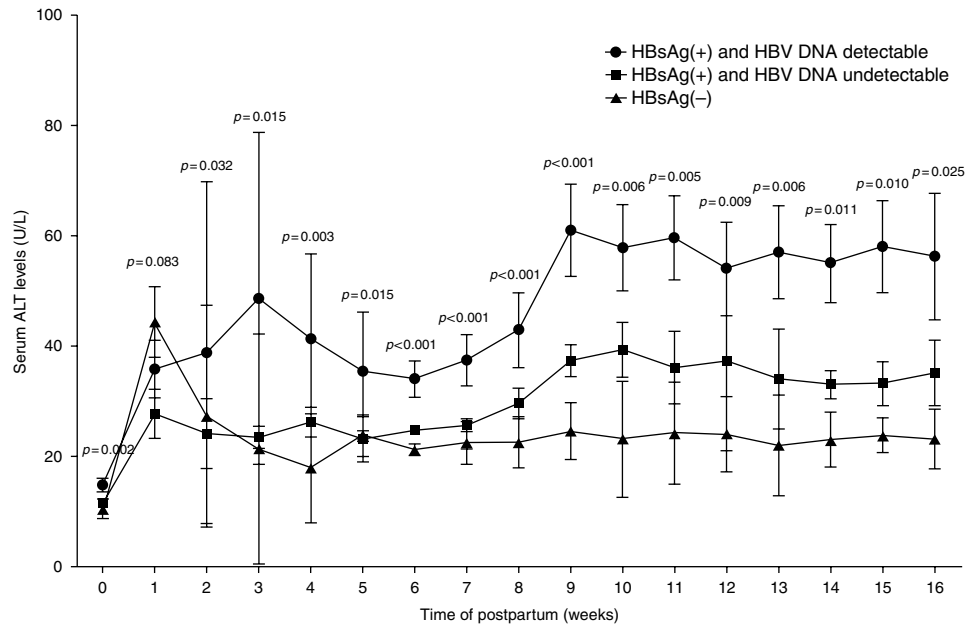


Fig. 2 Patterns of ALT level changes during the postpartum period in patients with and without HBV infection. ALT levels were elevated at postpartum week 1 in all the groups. Mothers without HBV infection presented with decreased ALT levels at week 2, and their levels remained within the normal range throughout the remainder of the study period. In contrast, mothers with HBV viremia demonstrated a bimodal pattern of elevated ALT levels, which peaked at postpartum weeks 3–4 and 9–12. ALT alanine aminotransferase, HBV hepatitis B virus, HBsAg hepatitis B surface antigen

weeks as the final observation point in this study to avoid missing important follow-up data because most patients were discharged from the clinic if their ALTs were normal in consecutive 12–16 weeks. Therefore, our results provide very important data over the 16 weeks postpartum, which is the real-life practice pattern for patients who do not have active CHB and those with CHB who do not need antiviral therapy.

In contrast to other studies that presented the mean or median ALT level for patients with flares, we defined clear categories and observed that ALT exacerbations (>10 times the ULN) were very rare (<0.1%) in patients with CHB but without detectable HBV DNA levels and in non-HBV infected patients. Our data suggested that mothers with detectable levels of HBV DNA at delivery are at a higher risk for exacerbations (3%) and should therefore be monitored more closely. Although ALT exacerbation might be an indication for antiviral treatment, we observed no hepatic decompensation or elevated bilirubin levels during these events. The symptoms associated with ALT events were mild to moderate, consistent with the results of previous studies [5, 6, 8, 9, 15]. In accordance with the majority of previously published reports, HBV serologic outcomes were not improved after ALT events in our study group. Further subgroup analyses demonstrated that ALT events occurred significantly more frequently in patients with HBeAg-positive status or detectable levels of HBV DNA, when compared to patients in other subgroups. We speculated that the ALT flares (or immune clearance) require certain levels of HBV replication as a trigger for the events. No such findings were reported in the retrospective study ($n = 101$) by Chang et al. [8], and HBV DNA levels were not linked to flares in the prospec-

tive study ($n = 126$) by Giles et al. [5] It is possible that these studies lacked the power to identify the above, although each study enrolled >100 mothers.

By using a mixed linear model [11], we identified a postpartum bimodal pattern of ALT events among mothers with hepatitis B with viremia. These findings suggest that monitoring visits should be scheduled at postpartum weeks 4 and 12, although more visits should ideally be scheduled. In previous studies, the independent risk factors for postpartum ALT events were not well characterized. In the study by Giles et al. [5], HBeAg positivity at baseline was not quite statistically significant for the prediction of postpartum flares in multivariate analysis [5]. Chang et al. did not observe any independent predictors in their study [8]. However, baseline levels of HBV DNA were not included in either of the aforementioned studies [5, 8]. In contrast, the multivariate analyses performed in the present study clearly demonstrated that ALT levels and HBV DNA levels at delivery were the only independent risk factors for postpartum ALT flares and exacerbations. In addition, our subgroup analyses according to different levels of HBV DNA identified the cut-off value of HBV DNA levels at delivery for predicting ALT events to be $5.01 \log_{10}$ IU/mL. Therefore, the measurement of ALT and HBV DNA levels at delivery should serve as a guide for postpartum follow-up and management.

The limitations of our study need to be acknowledged, with most of these limitations being related to the retrospective design of the study. In addition, the number of patients in the control group ($n = 869$) was less than those in the CHB groups ($n = 3367$) because our center is an infectious disease hospital and accepts patients with CHB as major referrals. The ratio of controls vs. cases

was about 1:4 and remained in a very reasonable ratio for the case-control study. Furthermore, we did not include HBsAg-negative and HbCAb-positive patients. According to the standard of care in our center, normal mothers (non-HBV infected) were required to undergo routine postpartum examinations at the obstetric clinic at 4–6 weeks after delivery. Blood tests, including blood chemistry tests and ALT level measurement, were performed. Patients with abnormal ALT levels were followed up every 4 weeks with blood tests until ALT levels normalized for 12 weeks. It is possible that we missed a few patients who might have had late elevation of ALT levels because their ALT levels were normal during the first 2 months of the postpartum period. Some cases of viremia were possibly missed in group B1 because the lower limit of quantitation was 100 IU/mL in our central laboratory. Despite the aforementioned limitations, the present study is still the largest study of its kind, with the best-defined population and most detailed data analysis.

In conclusion, the results of the current study revealed that in treatment-naïve CHB mothers, ALT flares and exacerbations mainly occur in those with HBV DNA levels $>5 \log_{10}$ IU/mL at delivery. Elevated ALT level or detectable levels of HBV DNA at delivery were independent risk factors for postpartum ALT events. Although 30% of treatment-naïve mothers with hepatitis B experienced ALT events, ALT levels were mildly to moderately elevated without severe clinical outcomes. The pattern of ALT elevations was bimodal, and postpartum monitoring at weeks 4 and 12 should be considered in clinical practice. Future large-scale, multicenter, prospective trials may be necessary to verify these findings.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Chronic hepatitis B (CHB) infection has negative impacts on pregnancy outcomes and increases pregnancy-related complications.
- ✓ Few studies have reported on the progression of CHB after delivery.

WHAT IS NEW HERE

- ✓ Mothers with CHB without treatment had a significantly higher frequency of alanine aminotransferase (ALT) flares or exacerbations after delivery.
- ✓ ALT levels peaked at postpartum weeks 3–4 and 9–12.
- ✓ Elevated ALT and detectable HBV DNA levels at delivery were independent risk factors of flares or exacerbations.
- ✓ A cut-off level of $5 \log_{10}$ IU/mL for HBV DNA at delivery predicted postpartum ALT events.
- ✓ The positive predictive value of this cut-off was 14.4%, with a negative predictive value of 98.2%.

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CONFLICT OF INTEREST

Guarantor of the article: Dr. Yao Xie.

Specific author contributions: WY, YX, and Z-YZ proposed the concept and supervised the data collection. CQP and WY contributed to the study design and performed the statistical analyses with support from GW. CQP wrote the manuscript with assistance from WY. CQP further revised the draft with inputs from all coauthors, performed critical reviews, communicated with the journal, and addressed comments from reviewers. WY, Y-WL, GW, M-HL, ML, and Y-HH contributed to data collection. All the authors vouch for the veracity and completeness of the data presented and agreed to submit the manuscript for publication.

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