Gastroenterology Report, 2024, **12**, goae091
https://doi.org/10.1093/gastro/goae091
Review Article

Review Article

Postpartum hepatitis flares in mothers with chronic hepatitis B infection

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Abstract

Postpartum elevation of alanine aminotransferase (ALT) in mothers with chronic hepatitis B (CHB) presents a significant clinical challenge. However, the existing literature demonstrates inconsistencies regarding its incidence and predictors in mothers infected with the hepatitis B virus (HBV). Recent advancements in antiviral prophylaxis against mother-to-child transmission of HBV and postpartum cessation of antiviral therapy further complicate this issue. Our literature review, spanning PubMed, and two Chinese-language databases (CNKI and Wanfang) from 1 January 2000 to 31 December 2023 aimed to consolidate and analyse available data on the frequency and severity of postpartum ALT flares, identify risk factors, and propose a management algorithm. Data from 23 eligible studies involving 8,077 pregnant women revealed an overall incidence of postpartum ALT elevation: 25.7% for mild cases, 4.4% for moderate cases, and 1.7% for severe cases. In the subgroup of mothers who were HBeAg-positive and on antiviral prophylaxis for preventing mother-to-child transmission, postpartum intermediate and severe ALT elevations were reported with pooled rates of 5.9% and 0.8%, respectively. Importantly, none resulted in mortality or necessitated liver transplantation. Identified risk factors for postpartum ALT flares in mothers with CHB included HBV DNA levels, ALT levels during pregnancy, postpartum cessation of antiviral treatment, and HBeAg status. By leveraging this evidence and recent data on predictors of intermediate or severe postpartum ALT flares, we propose a risk-stratified algorithm for managing postpartum ALT elevation and selecting therapy in mothers with CHB, tailoring different approaches for treatment-naive vs treatment-experienced populations. These recommendations aim to provide guidance for clinical decision-making and enhance patient outcomes.

Keywords: HBV; hepatitis flares; ALT elevation; liver inflammation; disease activation

Background

Controversies in postpartum ALT elevation

Postpartum elevation of alanine aminotransferase (ALT) in mothers with chronic hepatitis B (CHB) presents a significant clinical challenge due to the risk of disease progression and concerns about hepatic decompensation. However, the existing literature reveals inconsistencies regarding the frequency, timing, patterns of elevation, and predictors of ALT flares in mothers who are infected with hepatitis B virus (HBV). Recent advances in antiviral prophylaxis to prevent mother-to-child transmission (MTCT) of HBV and the postpartum cessation of antiviral therapy in mothers without indications for CHB treatment add further complexity. Additionally, postpartum ALT elevation has been observed in healthy mothers, complicating the clinical determination of the threshold for abnormal ALT levels.

ALT levels in mothers without hepatitis B infection

Postpartum ALT elevation in healthy mothers has been studied to varying extents, with evidence suggesting a multifactorial etiology [1]. While ALT elevation is commonly associated with liver injury [1, 2], its occurrence in some healthy mothers postpartum is not fully understood because ALT levels tend to decrease in the immediate postpartum period and return to pre-pregnancy levels within a few weeks after delivery in the majority of mothers [3]. Some research suggests that mild ALT elevations are common during the postpartum period, with reported incidence rates ranging from 3% to 20% in healthy women. However, severe elevations, defined as levels of >5–10 times the upper limit of normal (ULN), are less frequent, occurring in ∼0.1%–1% of cases [4]. Incidence rates may vary depending on factors such as maternal age, pre-existing health conditions, gestational age at delivery,

Received: 21 May 2024. **Revised:** 19 August 2024. **Accepted:** 17 September 2024

and mode of delivery. It is important to note that transient mild postpartum ALT elevation in mothers with or without CHB may not necessarily indicate liver injury but could instead represent normal fluctuations in liver enzyme levels.

Adaptive immune response and its impact on HBV infection

During pregnancy, the immune system undergoes significant adaptations to protect the fetus, recognized as a semi-allogeneic entity. This immune modulation involves a shift towards a more tolerant immune environment, characterized by increased regulatory T cells (Tregs) and decreased cytotoxic T-cell activity [5]. These changes help prevent fetal rejection but also influence liver physiology [6], particularly in women with CHB. The suppression of the immune response during pregnancy can lead to reduced liver inflammation and viral activity, often resulting in stable or decreased levels of ALT and HBV DNA [7].

In the postpartum period, the immune system rapidly reverts to its pre-pregnancy state, which can lead to immune reactivation. This rebound effect often triggers an increase in immune-mediated liver inflammation, potentially causing ALT flares and exacerbation of CHB. Several major changes have been reported, including a decrease in the number of Treg cells and an increase in the number of natural killer (NK) cells in the peripheral blood after delivery [8, 9]. Liver NK cells may cause liver inflammation through non-antigen-specific mechanisms. Additionally, the rapid decline in cortisol levels [9] after delivery, especially the enhanced HBV-specific T-cell response induced by HBV DNA and cytokines, is a primary cause of postpartum hepatitis [8, 10]. Therefore, the mechanism of postpartum hepatitis in pregnant women with hepatitis B is complex. A good understanding of these immune shifts is crucial for managing CHB in pregnant and postpartum women, as they are at heightened risk for liver complications during this period.

Challenges in managing ALT elevation in CHB mothers

Postpartum ALT elevation in mothers with CHB presents several challenges in understanding and managing the condition, directly impacting patient outcomes and healthcare delivery. First, distinguishing between normal postpartum liver transaminase changes and those indicative of pathological processes, such as the exacerbation of hepatitis B, can be challenging [11]. As discussed earlier regarding postpartum changes in ALT levels in healthy mothers, those with CHB could experience physiological changes in the postpartum period without hepatitis flares, including fluctuations in liver enzyme levels [3]. Second, there is a lack of high-quality data on the pattern of postpartum ALT elevation [12]. As a result, the timing of ALT monitoring is unclear. Determination of the optimal timing for postpartum ALT monitoring is essential for the detection of potential exacerbations of hepatitis B. Furthermore, systematic reviews are lacking on the frequency of monitoring and the duration of postpartum follow-up that is needed to detect significant changes reliably. Third, the dynamic changes in hormonal levels during pregnancy and postpartum and their impact on liver enzyme levels have not been fully explored [13, 14]. These changes could also potentially affect the course of hepatitis B. Understanding the interplay between hormonal changes and HBV activity is critical but remains an area of ongoing research [8]. Lastly, the long-term implications of postpartum ALT elevation in mothers with hepatitis B, for both maternal health and the risk of disease progression, are not well understood [15]. Long-term data are lacking on the impact of postpartum liver function changes on the natural history of hepatitis B and the development of liver-related complications, such as fibrosis and cirrhosis, or cancer risk over time [16].

Current postpartum management strategies

Since MTCT remains the primary global route for new HBV infections, efforts toward HBV elimination by 2030, as proposed by the World Health Organization, focus largely on reducing vertical transmission. Strategies include universal infant vaccination, administration of hepatitis B immune globulin to newborns of HBV-infected mothers, and updated guidelines for antiviral treatment during pregnancy [17, 18]. However, the complexity of postpartum ALT elevation is heightened by recent advancements in antiviral therapy for preventing MTCT of HBV, as some mothers have experienced hepatitis flares upon cessation of therapy after delivery [19–21].

Despite advances in preventing MTCT of HBV [22, 23], limited understanding persists regarding the prevalence and management of postpartum ALT elevation in HBV-infected pregnant women [24–26]. Recent literature presents divergent recommendations regarding the management of postpartum ALT elevation in HBV-infected women. Some recommend antiviral therapy for postpartum ALT levels that are at least five times the ULN, while others suggest that postpartum hepatitis in HBV-infected women tends to be self-limiting and does not require medical intervention [2, 27–30]. Most studies emphasize close monitoring of postpartum ALT in HBV-infected women and suggest intervention when necessary [2, 4, 27–32], but detailed methodologies are lacking. Hence, there is an urgent need to consolidate and summarize clinical management recommendations for postpartum ALT elevation in HBV-infected pregnant women.

Currently, no optimal management strategies have been proposed by international professional guidelines or World Health Organization guidelines regarding postpartum ALT elevation or hepatitis B flares in mothers with CHB [17, 24–26]. Current global guidelines recommend close monitoring of maternal ALT levels until 6 months postpartum[17, 24, 26], applying treatment standards that are similar to those for regular HBV patients[33, 34], without offering explicit recommendations for addressing postpartum ALT elevation in pregnant women with altered immune status [24–26]. Although the exact mechanisms that trigger postpartum ALT elevation remain elusive, most studies suggest a connection to the restoration of immune tolerance post-delivery [8, 35]—a phenomenon that may persist for up to a year after childbirth [8, 31, 35–37]. Therefore, HBV-infected women who are experiencing postpartum ALT elevation may require extended monitoring and even intervention if significant flares occur [36–38].

Objective of the review

The establishment of optimal strategies requires interdisciplinary collaboration between hepatologists, obstetricians, pediatricians, and researchers to improve our understanding of postpartum ALT elevation in mothers with hepatitis B and to develop evidence-based management approaches that are tailored to this population [39]. Therefore, we conducted the current comprehensive literature review to provide a summary of the evidence and updated insights into managing postpartum ALT flares. We anticipate that this review will assist clinicians in making balanced decisions between the need to control maternal disease activity and minimizing potential harm to the infant, particularly during breastfeeding. By drawing upon the available evidence, an algorithm for managing postpartum ALT elevation and hepatitis B flares is proposed for mothers with CHB.

Data selection process

Definitions

To clarify the discussion, the authors employed the following definitions for postpartum hepatitis B flares in CHB mothers without hepatic decompensation: (i) mild ALT elevation, defined as ALT levels above the ULN but less than five times the ULN; (ii) hepatitis B flare, defined as ALT elevation at levels equal to or above five times the ULN but less than 10 times the ULN; and (iii) severe hepatitis B flare, defined as ALT elevation at levels equal to or above 10 times the ULN. Mothers who exhibit clinical features of hepatic decompensation should be referred to a liver transplant center or an institution with liver experts available for management. The scope of our review does not encompass the management of decompensated patients.

Database and literature selection

The literature search encompassed PubMed and two Chinese-language databases (CNKI and Wanfang) from 1 January 2000 to 31 December 2023, seeking publications in English or Chinese (Figure 1). Keywords such as "Chronic Hepatitis B," "Postpartum Period," "Alanine Transaminase," "ALT Elevation," "Symptom Flare Up," "Abnormal Liver Function," and "HBV" were utilized to identify relevant publications based on the following criteria: (i) inclusion of pregnant women diagnosed with hepatitis B; (ii) investigation focusing on postpartum alanine transaminase or hepatitis flare; and (iii) reporting of clinically relevant outcomes. Studies were excluded if (i) mothers had co-infection with hepatitis A, C, D, E viruses, autoimmune hepatitis, or human immunodeficiency virus; (ii) mothers had pregnancy-specific liver diseases, particularly acute fatty liver of pregnancy, gestational diabetes mellitus, pregnancy-induced hypertension, intrahepatic cholestasis of pregnancy, or HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome; (iii) patients had liver cirrhosis or hepatocellular carcinoma; (iv) the study involved animal studies or translational research; (v) publications were reviews, meta-analyses, or case reports; or (vi) studies in which antiviral treatment during pregnancy was unclear.

Data search process

The literature search was conducted by three authors (Y.G., G.Q., and H.D.). Each author independently generated a list of eligible studies based on the screening of titles and abstracts, and independently extracted data from the selected publications. The first author (S.O.Y.) and the fourth author (Y.D.) verified the data screening and extraction. Any disagreements regarding data

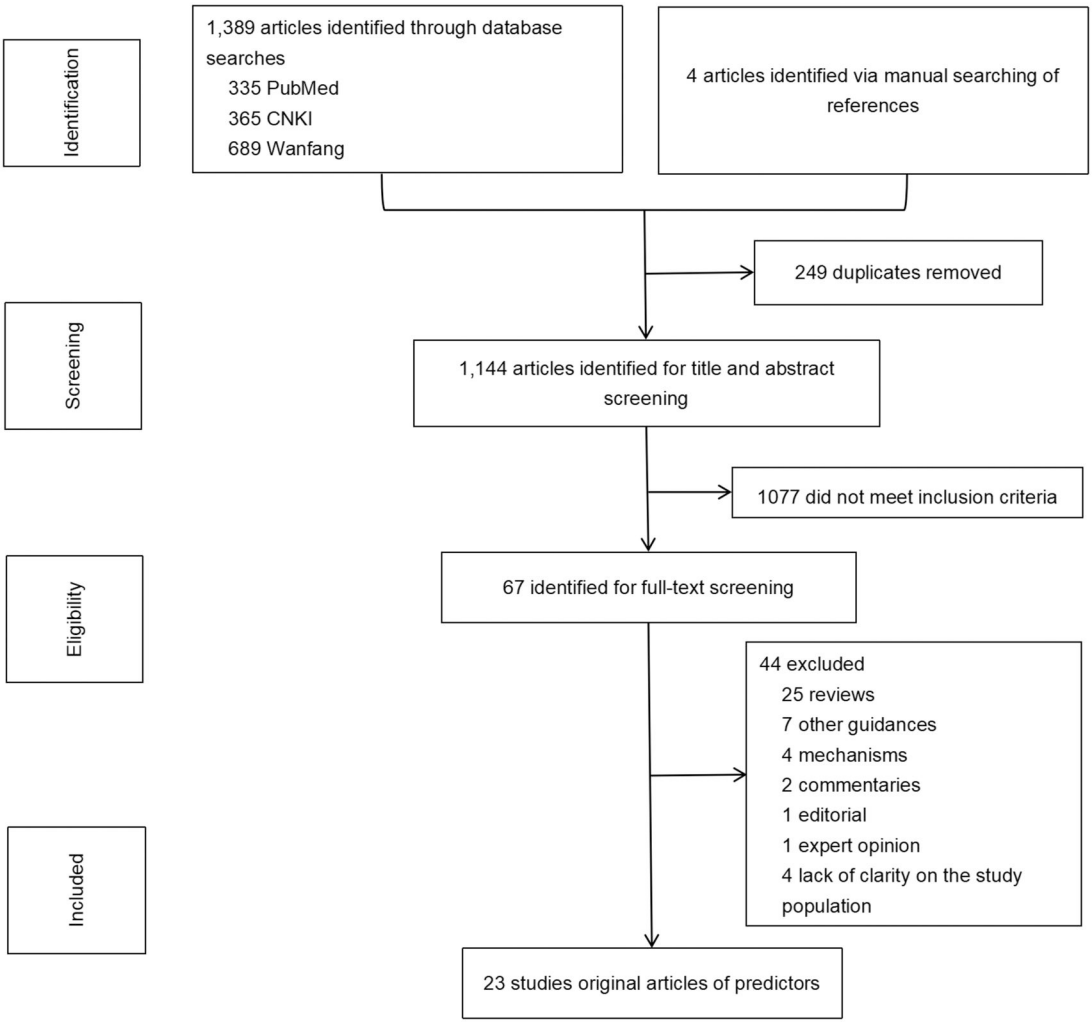

Figure 1. Data search and selection process. The literature search encompassed PubMed and two Chinese-language databases (CNKI and Wanfang) from 1 January 2000 to 31 December 2023, seeking publications in English or Chinese. Based on the pre-specified search term, relevant articles (n = 1,389) were identified initially. Among these articles, 23 met the eligibility criteria and were included in the current review. CNKI = China National Knowledge Infrastructure.

selection or extraction were resolved through discussions with the corresponding author (C.Q.P.). Discrepancies in study selections were ultimately resolved by group consensus. The extracted literature primarily included information such as the date of publication, article types, study centers, patient population, study design, sample size, treatment regimens before hepatitis flare, study period, risk factors for hepatitis flares, the occurrence of complications, treatment methodologies before and after delivery, the incidence of postpartum hepatitis flares, the timing of postpartum ALT elevation, the severity of the ALT flares, study conclusions, and study implications.

Data review and outcome of interest

This review focused on three primary outcomes: (i) the incidence of ALT elevation and hepatitis flares, (ii) the severity of ALT elevation or hepatitis flares, and (iii) the risk factors associated with ALT elevation or hepatitis flares. The current review categorized data into two distinct groups based on the intervention during pregnancy: (i) non-antiretroviral therapy during pregnancy and (ii) antiviral therapy during pregnancy. Following a thorough literature review and data analysis, the authors proposed a management algorithm for these patients based on the available data and evidence.

Literature reviews

Characteristics of the studies selected

Based on the search term, initially, 1,389 relevant articles were identified. Among these articles, 23 met the eligibility criteria and were included (Figure 1). The majority of studies were conducted in China (20/23) and the remaining articles originated from the USA (2 articles) and Greece (1 article). Twelve of the included studies were retrospective and 11 were prospective. Among the 8,077 mothers who were included in these 23 publications, the average age ranged from 27 to 33 years, with a mean age of 29.3 years. Among them, 3,650 mothers received antiviral treatment during pregnancy whereas 4,427 mothers did not receive any treatment. Twelve studies focused on HBeAg (+) pregnant women, whereas only two studies focused solely on HBeAg (–) patients. Nine studies included both HBeAg (+) and HBeAg (–) patients, with HBeAg (+) patients representing 8.0%–98% of cases; among them, three studies had >50% HBeAg (+) patients. Two studies did not specify the HBeAg status. A summary of the characteristics of the included articles and patient demographics is presented in Supplementary Table S1.

Incidence of postpartum ALT elevations

The frequency of postpartum elevations in ALT levels varied across reviewed studies, encompassing mild, moderate, and severe elevations. Reported incidences ranged from 4.2% to 47.3% for mild elevations, 3.5% to 32.5% for moderate elevations, and 0.8% to 1.7% for severe elevations (Table 1). The pooling of data from 23 studies revealed an overall incidence of ALT elevation of 25.7% (2,124 out of 8,279) for mild cases, 4.4% (181 out of 4,143) for moderate cases, and 1.7% (70 out of 4,143) for severe cases. Notably, none of the studies reported instances of mortality or necessitated liver transplantation.

It is noteworthy that the majority of studies (82.6%, 19 out of 23) defined the ULN ALT as 40 U/L (Supplementary Table S1). However, the threshold for ALT elevation that was indicative of hepatitis B flare varied among the studies, ranging from one time to five times above the ULN. Additionally, subgroups that were based on the HBeAg status or antiviral treatment status of patients during pregnancy exhibited differing incidences and severities of ALT elevation. Consequently, we stratified patients according to HBeAg status and antiviral treatment status during pregnancy for further examination and summarized data (Table 2).

Postpartum ALT elevation in treatment-naive mothers

A total of 4,427 treatment-naive patients were involved in 9 out of 23 studies [4, 30, 32, 40–45]. The pooled incidences of postpartum ALT elevation were 23.8% (1,054 out of 4,427) for mild cases, 3.3% (145 out of 4,427) for moderate cases, and 1.5% (65 out of 4,427) for severe cases. When stratifying by HBeAg status, the pooled incidences of postpartum ALT elevation in HBeAg-positive mothers vs HBeAg-negative mothers were 52.5% (348 out of 663) vs 13.1% (35 out of 267), $P < 0.001$. All treatment-naive patients with available HBeAg status were reported to have a mild elevation of ALT if the event occurred after delivery (Table 2). HBeAg-positive mothers had an odds ratio of 7.2 [95% confidence interval (CI), 5.0–10.8] when compared with HBeAg-negative mothers for the development of postpartum ALT elevation. However, in a study by Yi *et al.* [4] that enrolled 3,367 treatment-naive HBsAg-positive mothers without specified HBeAg status, the incidences of postpartum ALT moderate and severe elevation were reported in 3.5% and 1.7% of mothers, respectively [4]. This large study observed that the significant ALT events in treatment-naive mothers were <4% regardless of HBeAg status. In comparison, there was one study that enrolled healthy pregnant women and reported on the incidence of mild, moderate, and severe postpartum ALT elevations in 19.1%, 1.2%, and 0.1% of healthy mothers without HBV infection, respectively. However, the risk factors for these events were not fully explored.

Regarding the peak, patterns, and duration of postpartum ALT elevations in treatment-naive mothers, these nine articles point to some directions of the elevation occurring mainly within 12 weeks postpartum despite the findings being inconsistent [4, 30, 32, 40–45]. In addition, fewer studies discussed the frequency, timing, and duration of monitoring in these mothers, although all suggested antiviral therapy as needed. The data on the peak time and patterns of postpartum ALT elevation were very limited due to the different study durations and monitoring schedules, which varied from within 6 weeks to 1 year postpartum for the duration and blood tests every 4 to 24 weeks for monitoring. In HBeAg-positive mothers, a retrospective study in China observed a significantly higher incidence of ALT elevation (serum levels >40 U/L) within 42 days when compared with that at 7 months after delivery [25.5% (26/102) vs 2.1% (2/95), $P < 0.001$] [43]. Similar findings were noted in a prospective cohort study by Li *et al.* [20], showing an ALT elevation rate of 28.1% (27/96) within 12 weeks postpartum. Remarkably, a study by Quan *et al.* in China [32] reported a considerably high rate of postpartum ALT abnormalities that reached 70.6% (the majority were less than five times the ULN defined as 40 U/mL) within 6 weeks postpartum (at the end of the study) in this subgroup of mothers.

Similar findings on the onset time frame of ALT elevation or hepatitis flares were observed in studies that enrolled HBeAg-negative treatment-naive mothers. Elefsiniotis *et al.* [30] in Greece followed mothers every 3 months during the first year after delivery and every 6 months a year after. They reported an incidence rate of 29.6% (8/27) ALT elevation, mainly within the first 12 weeks after delivery; however, the sample size was small. In a large study by Yi *et al.* [4] on 3,367 HBsAg-positive Chinese mothers without antiviral therapy during pregnancy, mothers were followed up to 16 weeks postpartum and presented with 20.4%

Table 1. Pooled data on the incidence, severity, and timing of postpartum ALT flares

Subgroup patients with ALT elevation	Number of studies/total reviewed (*n*/*N*)	ALT elevation/all patients (*n*/*N*)	Incidence of ALT elevation [%, (95% CI)]	Liver decompensation or death	Detected time postpartum (weeks)
Treatment-naive mothers					
Mild elevation in HBeAg (+) [32, 40–43]	5/23	314/663	47.3 (43.5–51.5)	0	6–48
Mild elevation in HBeAg (–) [30, 44]	2/23	35/267	13.1 (9.1–17.1)	0	4–12
Mild elevation, unspecified HBeAg [4, 45]	2/23	705/3497	20.2 (18.9–21.5)	0	0–24
Moderate elevation in HBeAg (+) [32]	1/23	27/170	15.3 (9.9–20.7)	0	6
Moderate elevation in HBeAg (–)	0/23	N/A	N/A	N/A	N/A
Moderate elevation, unspecified HBeAg [4]	1/23	118/3367	3.5 (2.8–4.1)	0	16
Severe elevation in HBeAg (+) [32]	1/23	7/170	4.1 (1.1–7.1)	0	6
Severe elevation in HBeAg (–)	0/23	N/A	N/A	N/A	N/A
Severe elevation, unspecified HBeAg [4]	1/23	58/3367	1.7 (1.3–2.1)	0	16
ALT elevation without specified severity	0/23	N/A	N/A	N/A	N/A
Mothers received antiviral prophylaxis for preventing MTCT during pregnancy[a]					
Mild ALT elevation in HBeAg (+)	10/23	783/2364	33.1 (31.2–35.0)	0	6–52
Mild ALT elevation in HBeAg (–)	0/23	N/A	N/A	N/A	N/A
Mild ALT elevation, unspecified HBeAg [29, 46, 50–53]	6/23	276/878	31.4 (28.3–34.5)	0	6–48
Moderate ALT elevation in HBeAg (+) [32, 42]	2/23	36/606	5.9 (4.0–7.8)	0	6–42
Moderate ALT elevation in HBeAg (–)	0/23	N/A	N/A	N/A	N/A
Moderate ALT elevation, unspecified HBeAg	0/23	N/A	N/A	N/A	N/A
Severe ALT elevation in HBeAg (+) [32, 42]	2/23	5/606	0.8 (0.1–1.5)	0	6–42
Severe ALT elevation in HBeAg (–)	0/23	N/A	N/A	N/A	N/A
Severe ALT elevation, unspecified HBeAg	0/23	N/A	N/A	N/A	N/A
ALT elevation with no definition of severity	0/23	N/A	N/A	N/A	N/A
Mother receiving antiviral therapy for therapeutic purposes during pregnancy					
Mild ALT elevation in HBeAg (+) [41]	1/23	2/48	4.2 (−1.5 to 9.9)	0	0–24
Mild ALT elevation in HBeAg (–)	0/23	N/A	N/A	N/A	N/A
Mild ALT elevation, unspecified HBeAg [54]	1/23	9/562	1.6 (0.6–2.6)	0	28

[a] In this group, 92% of pregnant women took oral antiviral drugs solo for the purpose of preventing MTCT.
MTCT = mother-to-child transmission, ALT = alanine aminotransferase, N/A = data not available, HBeAg = hepatitis B e-antigen, CI = confidence interval.

Table 2. Comparison of postpartum ALT elevation at different time points of antiviral cessation

Author (published year)	Time points of antiviral cessation	Post-delivery follow-up	Definition of ALT flares	Patterns (peak)	Incidence of postpartum ALT flares, *n*/*N* (%)	*P*-value	Suggestion of antiviral cessation
Feng (2023) [50]	pp 12 wks vs pp 96 wks	96 wks	ALT > ULN (40 U/L)	24 wks	37/65 (56.9) vs 26/66 (39.4)	0.045	pp 18 months
Li (2023) [20]	At birth vs pp 6 wks	24 wks	ALT > 2 × ULN (80 U/L)	12 wks	31/131 (23.7) vs 9/37 (24.3)	0.738	N/A
Li (2021) [48]	At birth vs pp 12 wks	24 wks	ALT > 2 × ULN (80 U/L)	12 wks	9/35 (25.7) vs 8/31 (25.8)	>0.05	birth
Peng (2019) [47]	At birth vs pp 4–12 wks	24 wks after discontinuation	ALT > ULN (40 U/L)	24 wks after discontinuation	22/50 (44.0) vs 23/41 (51.6)	0.251	birth

ALT = alanine aminotransferase, ULN = upper limit of normal, pp = postpartum, wk = week, N/A = data not available.

(825/3,367), 3.5% (118/3,367), and 1.7% (58/3,367) of mild, moderate, and severe ALT elevation, respectively (Table 2). Although the incidence of ALT elevation might be overestimated for HBeAg-negative patients, as the study was retrospective and without specified HBeAg status (but 1,439/3,367 of CHB patients had undetectable HBV DNA and were likely to have been HBeAg-negative), the investigators observed that postpartum ALT elevations exhibited a bimodal pattern, peaking at 3–4 and 9–12 weeks postpartum, which was similar to that presented in HBeAg-positive patients.

Predictors for postpartum ALT flare in treatment-naive mothers

Among the 23 articles that were reviewed, 11 [4, 20, 30, 32, 40–43, 45–47] analysed risk factors for postpartum ALT elevation in treatment-naive mothers (Table 3). The independent risk factors were identified in five studies [4, 30, 32, 40, 41] through multivariate analyses, which included low levels of HBeAg, elevation of ALT, HBV DNA of >10,000 IU/mL, and high levels of HBcAb during pregnancy.

Postpartum flares in mothers with antiviral prophylaxis during pregnancy

A total of 3,848 patients were included in 16 out of 23 related articles [19–21, 29, 32, 37, 40, 42, 46–53] that investigated antiviral prophylaxis for the prevention of MTCT during pregnancy. The incidence of postpartum ALT elevation ranged from 15.8% to 60% within 52 weeks postpartum (Supplementary Table S1). Among HBeAg-positive mothers who received antiviral prophylaxis for the prevention of MTCT, 33.1% of them had postpartum mild ALT elevation in the pooled analysis of 10 studies [19–21, 32, 37, 40, 42, 47–49]. The occurrences of postpartum moderate and severe ALT elevations were only reported in two studies [32, 42] that enrolled HBeAg-positive mothers on antiviral prophylaxis

Table 3. Independent risk factors reported by studies for postpartum ALT elevations

Predictors categorized by severity	Independent predictors, OR (95% CI)	Factors not found to be associated with ALT flares
Treatment-naive mothers		
Mild ALT elevation	i) HBeAg {OR 0.19 (0.01–0.47) [40]} ii) HBV DNA > 4.0 $\log_{10}$ IU/mL {OR 57.02 (N/A) [41]} iii) ALT elevation during pregnancy {OR 1.07 (1.04–1.10) [32]; OR 266.40 (77.32–917.81) [30]} iv) HBcAb {OR 1.21 (1.10–1.34) [32]}	i) Mode of delivery [20, 42, 43] ii) Maternal age [43, 46, 47] iii) ALT during pregnancy [42, 43] iv) HBeAg [42, 43, 45] v) HBV DNA [20, 42, 43, 45]
Moderate ALT elevation	i) Elevated ALT in pregnancy (N/A) [4] ii) HBV DNA > 5.0 log10 IU/mL, (N/A) [4]	
Severe ALT elevation	i) Elevated ALT in pregnancy, (N/A) [4] ii) HBV DNA > 5.0 log10 IU/mL, (N/A) [4]	
Non-specified on the severity	N/A	
Treatment-experienced mothers		
Mild ALT elevation	i) HBeAg: OR 4.22 (1.25–8.27) [50]; OR 0.19 (0.07–0.47) [40]; OR 1.00 (1.00–1.01) [21, 46]; OR 0.26 (0.08–0.88) [52]; OR 2.55 (1.04–6.20) [29]; OR 2.13 (1.01–3.22) [46] ii) ALT elevation in pregnancy: OR 5.03 (1.24–20.44) [50]; OR 1.05 (1.02–1.07) [40]; OR 1.09 (1.02–1.16) [51]; OR 1.05 (1.01–1.08) [21]; OR 1.04 (1.02–1.05) [48]; OR 4.42 (1.2–15.7) [41]; OR 1.03 (1.04–1.10) [32]; OR 1.03 (1.00–1.06) [42] iii) Postpartum HBeAg drop ≥ 50% compared to baseline: OR 3.58 (1.39–9.19) [50] iv) HBcAb: OR 1.21 (1.10–1.30) [32] v) HBV DNA: OR 2.35 (1.10–5.00) [54]; OR 1.72 (1.39–2.26) [49]; OR 1.89 (1.40–2.50) [19] vi) Age: OR 0.87 (0.76–0.96) [21]; OR 0.91 (0.85–0.97) [29] vii) GDM: OR 0.32 (0.10–0.70) [52] viii) IL-10: OR 10.89 (1.20–100.20) [37] ix) Gestational age to start antiviral: OR 0.68 (0.22–1.56) [53]; OR 1.22 (1.05–1.43) [46] x) Anti-HBV therapy: OR 0.36 (0.21–0.60) [32] xi) Continuous TDF treatment: OR 0.31 (0.13–0.74) [50] xii) TBIL: OR 0.84 (0.76–0.94) [32] xiii) ALB: OR 0.91 (0.83–0.99) [40] xiv) PLT: OR 0.99 (0.99–1.00) [40] xv) NE%: OR 0.98 (0.97–0.99) [40]	i) Mode of delivery [19, 20, 42, 48] ii) Maternal age [19, 20, 42, 48] iii) Antiviral therapy during pregnancy [20] iv) HBV DNA level before delivery [20, 48] v) Cessation of antiviral therapy after delivery [54] vi) ALT [52] vii) HBeAg [42]
Moderate ALT elevation	N/A	
Severe ALT elevation	N/A	
Non-specified on the severity	N/A	

ALT = alanine aminotransferase, N/A = date not available, TDF = tenofovir disoproxil fumarate, GDM = gestational diabetes mellitus, TBIL = total bilirubin, ALB = albumin, PLT = platelet, NE = neutrophilic granulocyte, HBeAg = hepatitis B e-antigen.

for the prevention of MTCT with pooled rates of 5.9% and 0.8%, respectively (Table 1). Six studies [30, 46, 50–53] enrolled mothers without specifying HBeAg status and reported only mild postpartum ALT elevation of 31.4% of mothers in pooled analysis. In this subgroup, data were not available from a well-defined HBeAg-negative cohort on antiviral treatment during pregnancy. Hence, pooled analysis was not performed for comparison based on HBeAg status. Similarly, mothers who received antiviral treatment during pregnancy did not experience postpartum mortality or liver decompensation, mirroring outcomes observed in mothers without such treatment.

Impact of antiviral cessation on postpartum ALT elevation

Regarding the patterns of postpartum ALT elevation in this subgroup of mothers who were receiving antiviral for the prevention of MTCT, investigators might discontinue treatment after 12 weeks postpartum, as per international professional guidelines. The incidences of ALT elevation were reported to be ~50% in this subgroup [32, 37, 40, 47, 50, 51, 53]. The inconsistency of findings among studies (from 15.8% to 60%) could be due to variations in sample sizes, the definition of ALT abnormality, and the frequency of monitoring [19, 20, 49]. The majority of studies described postpartum ALT elevation within 6–12 weeks despite the coverage of antiviral treatment of ≤12 weeks postpartum in this subgroup of mothers. In mothers who did not indicate antiviral therapy after delivery, several studies [20, 47, 48, 50] compared the incidences of postpartum ALT elevation among cohorts of patients who discontinued antiviral treatment at different time points after delivery (Table 2). According to the data, the timing of antiviral cessation did not have a major impact on the significant levels of postpartum ALT elevation.

Postpartum ALT flares in mothers on antiviral treatment throughout pregnancy

Two studies described CHB mothers with antiviral treatment for maternal disease throughout pregnancy, enrolling HBeAg-positive mothers and non-specified HBeAg status in each of them [4, 30, 32, 40, 41]. All mothers continued the treatment during the postpartum study periods. Only mild ALT elevation with incidence of 4.2% and 1.6% was observed in HBeAg-positive and HBeAg unclassified mothers, respectively. However, there were no data available regarding the peak time and patterns of on-treatment ALT elevation due to the low frequency of the events.

For mothers who received antiviral treatment throughout pregnancy as indicated by active chronic hepatitis B and anticipated long-term treatment after delivery, the frequency of postpartum ALT elevation on antiviral treatment (on-treatment ALT

flare) was lower than that for mothers who received antiviral prophylaxis for MTCT and discontinued the therapy postpartum (ranging from 15.8% to 60%) [32, 37, 40, 47, 50, 51, 53], highlighting the increased frequency of mild postpartum ALT elevation after antiviral cessation.

Predictors for postpartum ALT flare in antiviral-treated mothers

Among mothers who received antiviral therapy during pregnancy, independent factors were investigated in 17 out of 23 studies [19–21, 29, 32, 37, 40–42, 46, 48–54] reviewed. In addition to the risk factors found in treatment-naive mothers, the following independent predictors were proposed in mothers who received antiviral therapy during pregnancy: postpartum HBeAg-level reduction of >50% of the levels at baseline before antiviral treatment, older age, history of gestational diabetes, high serum levels of IL-10, low levels of total bilirubin, low levels of albumin, low platelet counts, and the cessation of antiviral therapy after delivery (Table 3).

The conflicting findings regarding the role of HBeAg status or levels as an independent predictor of postpartum ALT elevation present divergent perspectives across different studies. Kushner *et al.* [55] conducted a retrospective analysis that involved 310 pregnant African women who received antiviral therapy before or during pregnancy, identifying HBeAg positivity as an independent risk factor for postpartum ALT elevation. Similarly, Zhou *et al.* in China [46], through a retrospective study of 103 pregnant women who were receiving antiviral therapy during pregnancy, observed that higher baseline e-antigen titers during pregnancy were associated with ALT elevation at 6 weeks postpartum. Conversely, several other studies that were conducted in China presented contrasting results, suggesting that low HBeAg levels (<3.1 logIU/mL) at delivery [21] or low HBeAg titer (< 258 S/CO) at the time of discontinuing antiviral drugs after delivery [40, 53] were independent factors that influenced postpartum ALT elevation. It is important to note that these discrepant conclusions arise from variations in the timing of HBeAg-level assessments, ranging from the early trimester during pregnancy to a few weeks after delivery.

Management strategies proposed by association guidelines

A comparison of the latest international guidelines reveals that risk factors for postpartum hepatitis activity and ALT elevation differ (Table 4). The APASL (2022) guideline proposes that discontinuation of antiviral therapy and youthfulness in the population receiving antiviral therapy for hepatitis B before conception are risk factors [25], aligning with the conclusions of AASLD (2018) guideline [56]. Additionally, in the treatment-naive population, HBeAg positivity is identified as a risk factor for postpartum ALT abnormalities. However, the EASL (2017) guideline does not mention risk factors for postpartum hepatitis activity and ALT elevation [26]. Among the 23 articles that we reviewed, 8 articles suggested that the risk factors for postpartum ALT elevation related to HBeAg status or levels, five articles focused on HBV DNA titers, and only one article each discussed HBcAb, gestational diabetes, parity, and serum IL-10 levels. Fourteen articles proposed higher levels of ALT during pregnancy as a risk factor for postpartum ALT elevation, which was not mentioned in the aforementioned international guidelines. Hence, in addition to the need for reconfirmation of indicators such as HBV DNA and HBeAg, there is a greater need for higher-quality studies that explore the impact of ALT levels during pregnancy on predicting postpartum ALT elevation. Consideration of this indicator in the updated guidelines is crucial [25, 26, 56].

Major guidelines concerning the postpartum management strategy for women with CHB emphasize the need for close monitoring of HBV markers and liver function [25, 26, 56]. However, the frequency and timing of monitoring vary across guidelines [25, 26, 56]. The APASL (2022) guideline suggests monitoring for treatment-naive mothers or those who received antiviral therapy only for the prevention of MTCT until 24 weeks postpartum [25]. If severe ALT flare occurs, then antiviral treatment should be administered. This approach aligns with the management scheme for all mothers with CHB as proposed by the AASLD (2018) guideline but does not specify the frequency of follow-ups [56]. However, the AASLD (2018) guideline recommends follow-up frequency for mothers with CHB: monitoring hepatitis B status every 3 months for 24 weeks postpartum, consistently with the China (2023) guideline for the management of CHB [57]. The Chinese guidelines additionally propose the initiation of antiviral treatment if the ALT is at least five times the ULN or if hepatitis B activity is present—a point that is not addressed by the AASLD (2018) guideline [56, 57]. The postpartum management schemes for hepatitis B-infected pregnant women proposed by these guidelines lack consensus and specificity for different pregnancy statuses [25, 26, 56]. In this review, out of 23 articles, only 2 articles provided specific management recommendations for postpartum ALT elevation in hepatitis B-infected pregnant women who received antiviral treatment during pregnancy.

It is widely acknowledged that regular follow-up visits for hepatitis B-infected pregnant women should extend until 24 weeks postpartum [25, 56]. Mild elevations in ALT levels usually require rest and do not necessitate specific intervention, whereas moderate or severe elevations may warrant antiviral therapy [25, 26, 56]. However, studies have indicated instances of ALT abnormalities persisting for ≤1 year postpartum [50, 58], suggesting the need for a potential extension of follow-up duration in guidelines. Although guidelines attribute mild ALT elevation in postpartum women to immune and hormonal changes, they do not specify the range of elevated normal values [25, 26, 56]. Thus, there is a need for a comparative analysis between postpartum ALT levels in hepatitis B-infected and healthy pregnant women to draw more scientifically grounded conclusions. The current recommendations regarding the frequency of postpartum ALT follow-ups in major guidelines and scientific research lack consistency [25, 26, 56]. To prevent oversights, high-quality studies and expert consensus are urgently needed to guide clinicians in establishing scientifically rational postpartum follow-up plans and management strategies for hepatitis B-infected pregnant women.

Discussion

As of 2023, the latest global guidelines unanimously recommend the use of antiviral therapy during late pregnancy for HBV-infected pregnant women with HBV DNA of >200,000 IU/mL to reduce the risk of MTCT [17, 25, 26, 56]. Moreover, due to alterations in postpartum-specific immune functions, hormonal levels, and the discontinuation of medication by some pregnant women, there is an increased susceptibility to abnormal postpartum ALT levels. Therefore, there is an emphasis on the close monitoring of postpartum liver function regardless of antiviral therapy usage during pregnancy [17, 25, 26, 56]. However, further exploration is needed regarding the protocols and measures for postpartum monitoring. There is currently no consensus on the frequency

Table 4. Predictors proposed by the current guidelines and management recommendations

Guideline	Risk group definition	Monitoring	Definition of severity	Treatment indication	Therapy	Duration of treatment
EASL (2017) [62]	Not defined	Close monitoring of liver enzyme tests during the postpartum period (frequency and duration not specified)	Not defined	Significant ALT elevation, high viral load, or signs of liver decompensation	Tenofovir or Entecavir	Not specified
AASLD (2018) [56]	Not defined	Close monitoring of liver enzyme tests during the postpartum period (frequency and duration not specified)	Not defined	Significant ALT elevation or clinical symptoms suggestive of liver decompensation	Tenofovir or Entecavir	Not specified
APASL (2022) [25]	Not defined	Close monitoring of liver enzyme tests during the postpartum period (frequency and duration not specified)	Not defined	Significant ALT elevation, high viral load, or evidence of liver decompensation	Tenofovir or Entecavir	Not specified

ALT = alanine aminotransferase, EASL = European Association for the Study of the Liver, AASLD = American Association for the Study of Liver Diseases, APASL = Asian-Pacific Association for the Study of the Liver.

and duration of monitoring; international guidelines suggest one or two follow-up visits within the first 24 weeks postpartum [17, 25, 26, 56]. Additionally, there remains controversy surrounding the necessity for treatment for postpartum abnormal ALT levels or at what threshold ALT elevation treatment should be initiated.

Our review findings indicate that, among pregnant individuals who did not receive antiviral treatment during pregnancy, the occurrence rate of abnormal ALT within 48 weeks postpartum ranged from 11.3% to 70.6%, displaying a bimodal trend, with peaks at postpartum Weeks 6 and 12, primarily concentrated in the mild elevation range. Among these groups, the occurrence rate of postpartum ALT abnormalities was higher in the HBeAg-positive population than in the HBeAg-negative or mixed HBeAg status subpopulations. Our pooled analysis reported an odds ratio of 5.7 with a 95% CI of 3.8–8.4 when comparing HBeAg-positive mothers with HBeAg-negative mothers. This is primarily attributed to the association of HBeAg positivity with higher HBV DNA levels, which may trigger a stronger immune response leading to liver inflammation and damage, subsequently resulting in elevated ALT levels [55]. Risk factors for postpartum ALT elevation include lower levels of HBeAg during delivery, higher ALT levels during pregnancy, high HBV DNA (>10,000 IU/mL), and high levels of HBcAb at delivery.

In contrast to the latest global guidelines [17, 26, 56], only the APASL (2022) and China guidelines (2023) provide specific recommendations for this population [25, 57], suggesting follow-ups at 24 and 6–8 weeks postpartum, respectively. However, a summary of existing research results reveals that ALT abnormalities can persist for ≤1 year postpartum [50, 58]. Therefore, this review suggests that clinicians should consider extending follow-up times to 1 year postpartum with a frequency of every 6 weeks [4, 50, 58], particularly emphasizing pregnant women with baseline HBeAg positivity, abnormal ALT during pregnancy, and HBV DNA of >10,000 IU/mL. Lower levels of HBeAg during delivery were associated with postpartum ALT abnormalities. While consistent with prior studies [31, 35] proposing that a decline in HBeAg to a certain cut-off value usually indicates the onset of immune clearance, the specific cut-off value and mechanism still require further exploration. The same applies to the risk factor of high levels of HBcAb, which could provide clinicians with more precise recommendations.

Although there is limited research analysing the occurrence rates of postpartum ALT elevation in healthy pregnant women, mild elevation was observed in 19.1% of cases, while the occurrence rates for moderate and severe elevation were 3.5% and 1.7%, respectively, with subsequent regressions toward normal levels. However, it is essential to further define the normal range and duration of postpartum ALT elevation in healthy pregnant women to offer crucial guidance to clinicians in managing postpartum ALT abnormalities in women with hepatitis B infection.

The review divided HBV-infected pregnant women who were receiving antiviral treatment during pregnancy into two subgroups: those undergoing antiviral treatment to prevent MTCT and those treated for active CHB. The results indicate that, among those aiming to prevent MTCT, individuals who discontinued antiviral medication within 12 weeks postpartum exhibited an incidence of subsequent ALT abnormalities ranging from 11.9% to 60.0% within 52 weeks of postpartum follow-up, predominantly around a 50% elevation. Peaks in ALT abnormalities were observed around postpartum Weeks 6–12 and 24, depending on the timing of medication cessation. In contrast, the incidence of ALT abnormalities was 39.4% among those who discontinued medication after 12 weeks or continued treatment, indicating a significantly higher rate in the former group compared with the latter. However, due to guidelines' recommending discontinuation of antiviral medication at 12 weeks postpartum for preventing MTCT, fewer women discontinued medication after 12 weeks postpartum, resulting in relatively limited research data available for formulating appropriate strategies. A recent meta-analysis by Pan *et al.* [59] supports the idea of discontinuing antiviral treatment at delivery rather than continuing it beyond 12 weeks postpartum. Delayed cessation of antiviral treatment does not significantly impact the frequency or severity of postpartum ALT flares, suggesting that extending antiviral therapy may not offer additional benefits in managing ALT abnormalities in mothers who have received antiviral therapy solely for the purpose of preventing MTCT.

The occurrence rate of postpartum ALT abnormalities among HBV-infected pregnant women with antiviral therapy throughout pregnancy and the postpartum period (continued treatment for maternal indications of CHB therapy) was lower, ranging from 1.6% to 4.2%. APASL (2022), China Guide (2023), and AASLD (2018) recommend follow-ups until 24 weeks postpartum for pregnant women who are orally taking antiviral drugs for MTCT prevention. Only the latter two mention a follow-up frequency of every 3 months (similarly for self-treatment women). Severe ALT

elevation warrants reinitiation of antiviral treatment. Based on our analysis, this review recommends that pregnant women who use antiviral medication during pregnancy should undergo follow-ups extending to 1 year postpartum. For women who discontinue medication postpartum, check-ups every 3 months are advised. As for women who do not discontinue medication, their initial examination should occur within 6–8 weeks postpartum, after which check-up intervals can be extended appropriately. By leveraging the evidence and recent data, we propose a risk-stratified algorithm for managing postpartum ALT elevation and selecting therapy in mothers with CHB, tailoring different approaches for treatment-naive vs treatment-experienced populations (Figure 2). These recommendations aim to offer guidance for clinical decision-making and enhance patient outcomes.

Several risk factors for postpartum ALT abnormalities among this population include high ALT and HBV DNA levels during pregnancy and younger age. While high HBV DNA levels align with the risk factors suggested by the Chinese guideline [57], high ALT levels during pregnancy and younger age are not included in international guidelines [17, 25, 56]. Kushner *et al.* [55] reported that, with every 5-year increase in age, there is a 30% reduction in the risk of HBV recurrence, yet the specific mechanism remains unclear. We speculate that this might be attributed to reduced immune tolerance in younger pregnant women after the release of maternal immune suppression postpartum. This reduced tolerance might lead to a stronger immune response when facing the HBV, potentially causing not only an impact on the virus, but also self-immune damage to liver tissue, consequently resulting in elevated ALT levels. Furthermore, the influence of higher ALT levels during pregnancy on postpartum ALT abnormalities is primarily due to the complex physiological changes in the maternal system during gestation [60], in which cellular immune functions tend to be suppressed, resulting in decreased ALT levels during pregnancy compared with non-pregnant states

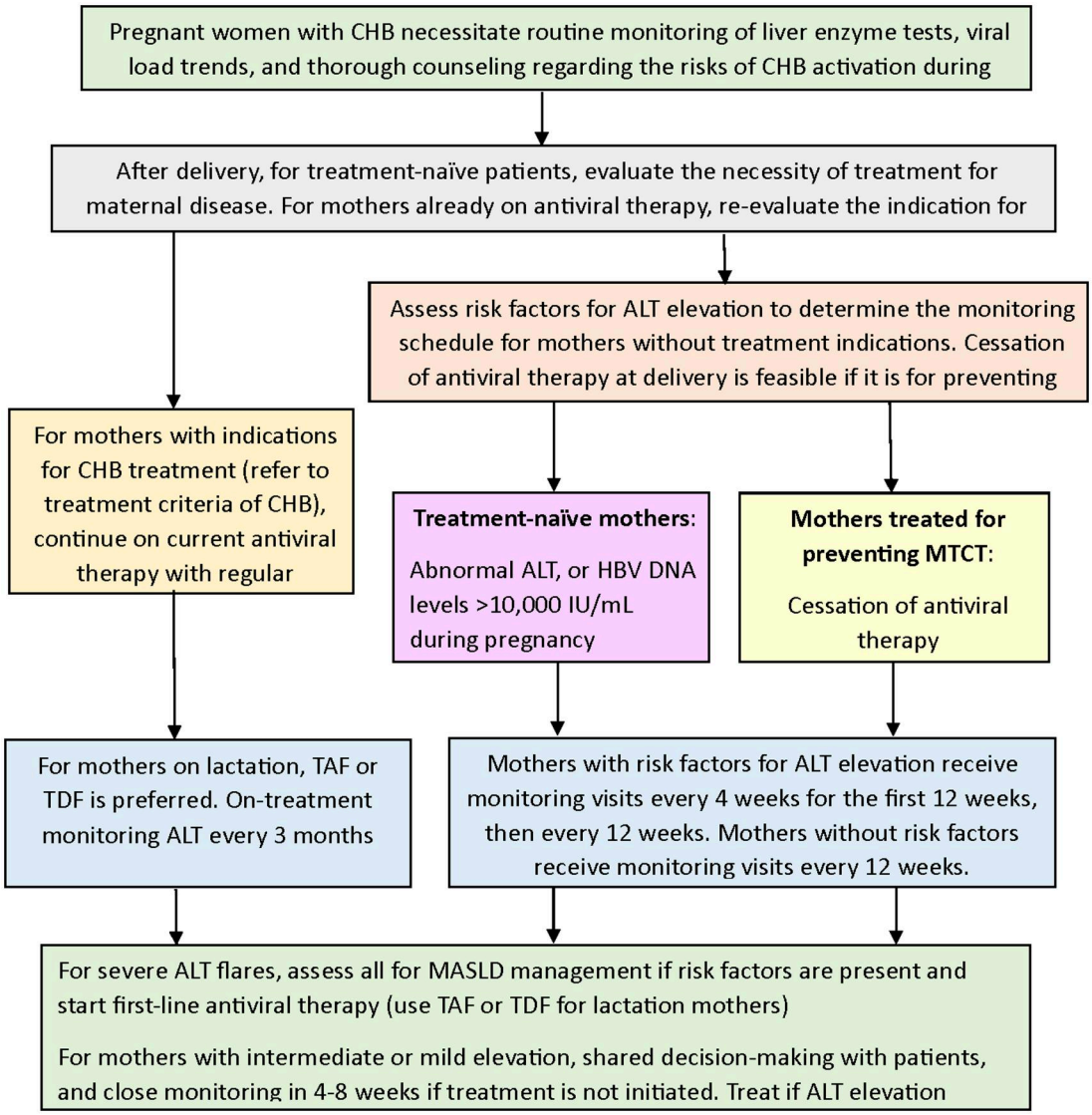

Figure 2. Management algorithm for postpartum ALT elevation in mothers with CHB. Risk-stratified algorithm for managing postpartum ALT elevation and selecting therapy in mothers with CHB, adapting different approaches for treatment-naive vs treatment-experienced populations. ALT elevation is defined by the authors as levels exceeding the local laboratory cut-off value or 40 U/L. Postpartum hepatitis B flares are classified into three scales among mothers without hepatic decompensation: mild ALT elevation (above ULN but less than 5 × ULN); intermediate ALT elevation (5 × ULN but less than 10 × ULN); and severe hepatitis B flare (>10 × ULN). ALT = alanine aminotransferase, ULN = upper limit of normal, CHB = chronic hepatitis B, MTCT = mother-to-child transmission, HBV = hepatitis B virus, TAF = tenofovir alafenamide, TDF = tenofovir disoproxil fumarate, MASLD = metabolic dysfunction-associated steatotic liver disease.

[27]. In this context, higher ALT levels during pregnancy might indicate an enhanced maternal immune response to HBV, leading to a recurrence of liver disease postpartum. Other less common factors include high levels of HBcAb, multiparity, a longer duration of HBV infection, late initiation of antiviral therapy during pregnancy, gestational diabetes mellitus, and elevated levels of IL-10. Further research is needed to confirm and elucidate the scientific validity and mechanisms behind these findings.

Limitations of the review and data gaps

During the review of postpartum ALT flare in mothers with hepatitis B from 23 articles, several significant data gaps emerged: (i) inadequate research or clinical data exist regarding the appropriate normal range of ALT during the postpartum period in both healthy mothers and those infected with hepatitis B [12, 29, 30]; (ii) the association between metabolic dysfunction and elevated ALT levels during the postpartum period has not been thoroughly investigated [61]; (iii) the pattern of fluctuations or elevations in ALT levels during the postpartum period has not been clearly defined [4, 21, 58, 61]; and (iv) the impact of postpartum ALT flare on liver inflammation and damage (disease progression) in mothers with hepatitis B remains uncertain [31].

The addressing of these data gaps necessitates further research studies or clinical investigations that are specifically tailored to understand the occurrence, risk factors, clinical significance, and management of postpartum ALT flare in mothers with hepatitis B. This may involve prospective cohort studies, retrospective analyses of existing datasets with well-defined patient populations, or clinical trials that are aimed at evaluating potential interventions or management strategies. By bridging this data gap, healthcare professionals can enhance their understanding of the specific challenges and considerations associated with managing hepatitis B in the postpartum period. This, in turn, could lead to improved outcomes for both mothers and their infants.

Summary

The overall incidence of postpartum ALT elevation in mothers with CHB was 26%, 4%, and 2% for mild, moderate, and severe cases, respectively. In highly viremic mothers who received antiviral prophylaxis for preventing MTCT, postpartum intermediate and severe ALT elevations were reported with pooled rates of 6% and 1%, respectively. Importantly, none resulted in mortality or necessitated liver transplantation. Identified risk factors for postpartum ALT flares in mothers with CHB included HBV DNA and ALT levels during pregnancy, postpartum cessation of antiviral treatment, and HBeAg status.

Based on the latest research, findings, and interpretation of newly published data, this review provides reliable data and management strategies for the occurrence of elevated postpartum ALT levels in HBV-infected pregnant women. Considering maternal safety, extending postpartum follow-up for HBV-infected women to ≥1 year is an inevitable choice for future clinicians. However, to acquire sufficient evidence and explore more specific risk factors for postpartum ALT abnormalities, further prospective studies on a larger scale and with longer follow-up periods are warranted.

Supplementary Data

Supplementary data is available at *Gastroenterology Report* online.

Authors' Contributions

C.Q.P. conceived the concept, designed the review, and outlined the study. Y.G., S.O.Y., G.Q., Y.D., and H.D. conducted the data screening, retrieval, and extraction. Y.G., S.O.Y., and C.Q.P. interpreted and analysed the data. Y.G. and C.Q.P. drafted the initial manuscript. S.O.Y. and C.Q.P. rigorously revised it. All authors contributed to the final version of the manuscript, and the corresponding author confirmed that all listed authors meet the criteria for authorship, with no other eligible authors omitted.

Funding

This study is supported by the "Belt and Road" Innovative Talent Exchange Project for Foreign Experts, sponsored by the Ministry of Science and Technology, China (G2022030048L); science and technology innovation strategy special fund project of Guangdong Province (pdjh2023b0433); and undergraduate capacity enhancement innovation project of Guangzhou Province (2022JXA003).

Conflicts of Interest

C.Q.P. received institutional research grants from Gilead Sciences and Wuxi Hisky Medical Technologies Co., Ltd. Other authors have no financial interests to be disclosed.

Data Availability

Materials are from published articles. All data supporting the findings of this narrative review are included in this published article.

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Gastroenterology Report, 2024, 12, –
https://doi.org/10.1093/gastro/goae091
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