

Serum Alanine Aminotransferase and Hepatitis B DNA Flares in Pregnant and Postpartum Women with Chronic Hepatitis B

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- OBJECTIVES:** Alterations in the immune system during pregnancy have been associated with reactivation of hepatitis B virus (HBV) in chronic hepatitis B (CHB) women. However, the effects of pregnancy on CHB remain not well understood. The goal of this study was to examine flares in HBV DNA and serum alanine aminotransferase (ALT) during pregnancy and postpartum in CHB women untreated prior to pregnancy.
- METHODS:** This was a multicenter retrospective study of 113 pregnancies in 101 CHB women who presented during pregnancy at two community gastroenterology clinics and two tertiary medical centers in the United States during 1997–2015. Outcomes analyzed included onset, severity, and resolution of flares in HBV and ALT that occurred prior to starting antiviral therapy, if antiviral therapy was subsequently initiated. Women who initiated antiviral therapy during pregnancy were not included in the analysis of postpartum flares.
- RESULTS:** HBV DNA flares were observed in 9% (8/90) of women during pregnancy and 4% (2/48) of women during postpartum. Flares in ALT (99–2522 U/l) were observed in 6% (7/112) of women during pregnancy and 10% (5/51) of women within the first 3 months of delivery. Age, HBeAg positivity, baseline HBV DNA, baseline ALT, gravida, and parity were not found to be significant predictors of flare.
- CONCLUSIONS:** Flares in HBV DNA and ALT can occur during late pregnancy and early postpartum in CHB women, and can be severe. Women with CHB should therefore be closely monitored during pregnancy and early postpartum.

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INTRODUCTION

Chronic infection with hepatitis B virus (HBV) affects more than 240 million individuals globally and can lead to serious complications, such as cirrhosis and hepatocellular carcinoma (1). Although universal maternal screening programs and immunoprophylaxis to newborns have greatly reduced mother-to-child transmission, immunoprophylaxis can fail in up to 30% of infants, with high maternal HBV DNA levels and HBeAg positivity being key risk factors (2–4). As a result, there has been growing support for the initiation of antiviral therapy during late pregnancy in

highly viremic women (5–8). Antiviral therapy may also be initiated to improve maternal outcomes, as immunological changes during pregnancy and postpartum can lead to acute liver failure in women (9).

During pregnancy, cell-mediated immunity is suppressed, possibly because of an increase in adrenal corticosteroids, estrogens, and progesterone, thereby allowing the woman to tolerate the semi-allogenic fetus (10,11). Postpartum, these changes are reversed. Increased susceptibility to some diseases, improved autoimmune hepatitis, and increased HCV RNA levels have all been observed

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during pregnancy (11–14), and several studies have also reported higher-than-expected HBeAg seroconversion rates (15) and high rates of alanine aminotransferase (ALT) increases during the initial postpartum period in HBV-infected women (5,16–20). Whereas most hepatic flares were mild and resolved spontaneously (17), severe cases including liver failure have been reported both during pregnancy and postpartum (9,21).

Thus, the goal of this study was to examine the rates and severity of virologic and biochemical reactivation both during pregnancy and the initial 6 months postpartum in women chronically infected with HBV who had not received antiviral therapy prior to pregnancy or flare, and to identify predictors for these flares.

METHODS

This was a multicenter retrospective study of chronic hepatitis B (CHB) women who presented during pregnancy at two community-based gastroenterology clinics, as well as gastroenterology or obstetric clinics at two tertiary medical centers, in the United States between 1997 and 2015. Patients were identified by their referring physician or by electronic query using combined HBV infection and pregnancy ICD-9 codes.

Laboratory tests (HBV DNA and ALT) were generally performed every 1–3 months during pregnancy, every 3–6 months postpartum, and more often in patients who had elevated HBV DNA or ALT. On the basis of the discretion of the physician and the patient and timing of flare or follow-up visit, antiviral therapy (lamivudine, tenofovir disoproxil fumarate, or telbivudine) was initiated during pregnancy or early postpartum.

Patients were included if they had not received antiviral therapy prior to pregnancy, and had baseline serum HBV DNA and at least two data points for the determination of a flare in HBV DNA or ALT during pregnancy or initial 6 months postpartum. Exclusion criteria included co-infection with hepatitis A, C, D, or human immunodeficiency virus. All clinical data available before, during, and after pregnancy were collected from patient charts using a patient case report form.

Baseline was defined as 1 year prior to the start of pregnancy, or the earliest point during pregnancy if pre-pregnancy data were not available. The primary end point for the determination of flare was the occurrence of flares during pregnancy and/or postpartum in the absence of antiviral therapy. If patients were initiated on antiviral therapy during pregnancy owing to flares, patients would be excluded from analysis of postpartum flares, even if these patients would discontinue therapy at delivery. Thus, data following the initiation of antiviral therapy was excluded, and women who initiated antiviral therapy during pregnancy were excluded from postpartum flare analysis. A flare in HBV DNA was defined as a minimum increase of 2 log IU/ml. ALT flare was defined as five times the upper limit of normal (ULN; 19 U/l) or $\geq 3\times$ baseline, whichever was higher. Severe flares were defined as an increase of 2 log IU/ml in HBV DNA and ALT $\geq 10\times$ ULN (≥ 190 U/l). Flares beginning during pregnancy that had not resolved by early postpartum were excluded from the analysis of postpartum flares. ALT flare resolution was defined as $\leq 2\times$ ULN or ALT prior to flare.

Statistical analyses

Chi-squared (χ^2) tests were used to evaluate categorical variables, and Student *t*-tests were used to evaluate continuous variables. Statistical significance was defined with a two-sided test and *P*-value of ≤ 0.05 . Univariate and multivariate logistic regression analyses were used to determine odds ratios, adjusted odds ratios, and their 95% confidence intervals to relate flare incidence to age, gravida, parity, HBeAg, baseline HBV DNA, and baseline ALT. All statistical analyses were performed using Stata version 11.2 (STATA Corporation, College Station, TX).

This study was approved by the Administrative Panel for Human Subjects at Stanford University and the institutional review board of the Beth Israel Deaconess Medical Center at Harvard Medical School.

RESULTS

We identified a total of 113 pregnancies in 101 expectant women with CHB who met inclusion criteria and did not receive antiviral therapy prior to pregnancy. Compared with low baseline HBV DNA women, women with high viral loads were younger (30 ± 5 vs. 33 ± 4 years, $P=0.0014$), had lower gravida ($P=0.004$) and parity ($P=0.01$), and were more likely to be HBeAg positive (57.6% vs. 10.3%, $P<0.0001$) (Table 1). The 105 pregnancies with known outcomes all resulted in live births.

Flares in HBV DNA and ALT during pregnancy

During pregnancy, flares in HBV DNA (≥ 2 log IU/ml increase) were observed in 9% (Table 2) of pregnancies, and were similar in high and low baseline HBV DNA women. ALT flares were observed in 6%, and were more frequent in high baseline HBV DNA women (7% vs. 5%, $P=0.702$). All ALT flares were severe (ALT $\geq 10\times$ ULN and increase in HBV DNA ≥ 2 log IU/ml), with hepatic decompensation occurring in one patient at week 33 of gestation (peak ALT 2522 U/l and total bilirubin 16.4 mg/dl). She underwent urgent cesarean delivery and was thereafter treated with entecavir resulting in resolution of her liver failure. Ultrasound elastography did not demonstrate advanced fibrosis or steatosis. All other women who flared in ALT during pregnancy, both treated (50%) and untreated (50%), also recovered following delivery.

Half of the women who flared in HBV DNA (50%, 4/8) subsequently initiated treatment during late pregnancy or within a week of delivery, including three women who had a concomitant flare in ALT. Most women who had ≥ 2 log IU/ml increases in HBV DNA during pregnancy and were not on antiviral therapy at the time of delivery or early postpartum also returned to baseline HBV DNA by 1-year postpartum (Figure 1). Interestingly, HBV DNA in one woman (subject 25) was significantly lower 1 year after delivery than at baseline (5.2 vs. 2.2 log IU/ml).

Flares in HBV DNA and ALT during postpartum

Only women who remained untreated during pregnancy were included in the analysis of postpartum flares. Flares that began during pregnancy and had continued postpartum were also excluded.

Table 1. Baseline characteristics and lab values

	Baseline HBV DNA ≤2,000 IU/ml (n=45)	Baseline HBV DNA >2,000 IU/ml (n=68)	P value
Age (years) ^a	33.4±4.4	30.3±5.1	0.0014
<i>Ethnicity</i>			0.003
Asian	84.4%	95.6%	
Hispanic	2.2%	1.5%	
Black	4.4%	2.9%	
Other	9.0%	0.0%	
BMI (kg/m ²) ^a	25.5±5.8	23.0±5.4	0.05
<i>Comorbidities</i>			
Diabetes mellitus	2.7%	11.5%	0.12
Hypertension	10.8%	8.3%	0.68
Hyperlipidemia	5.6%	8.2%	0.63
Gravida ^b	2 (1–4)	2 (1–2)	0.004
Gravida=1	40.0%	49.2%	0.34
Parity ^b	1 (0–2)	0 (0–1)	0.01
Parity=0	48.9%	62.1%	0.17
HBe antigen positive	10.3%	57.6%	<0.0001
HBV DNA (log IU/ml) ^a	2.1±0.8	6.2±2.0	<0.0001
Median (IQR)	2.2 (1.8–2.7)	6.7 (4.0–8.0)	
ALT (U/l) ^a	38±62	75±302	0.42
Median (IQR)	29 (19–34)	34 (22–49)	
AST (U/l) ^a	21±6	26±8	0.006
Alkaline phosphatase (U/l) ^a	65±18	66±24	0.83
Albumin (g/dl) ^a	4.1±0.4	4.2±0.3	0.22
Total bilirubin (mg/dl) ^a	0.6±0.2	0.6±0.2	0.65
Platelet count (K/μl) ^a	229±72	215±47	0.55
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HBV, hepatitis B virus; IQR, interquartile range.			
^a Mean±s.d.			
^b Median (IQR).			

Postpartum HBV DNA flares were observed at a median 9 weeks after delivery, in 9% of women with low baseline viral loads (Table 2). One woman, who also had a concomitant postpartum flare in ALT (175 U/l), recovered following initiation of antiviral therapy. Postpartum HBV DNA flares were not observed in high baseline viral load women who remained untreated throughout pregnancy.

Postpartum ALT flares (99–363 U/l) were observed in 10% (5/51) of women who had not received antiviral therapy during pregnancy, and occurred mostly during the first 3 months postpartum (Table 2). Postpartum ALT flares resolved with treatment in one case.

Antiviral therapy in patients with and without flare during pregnancy

Among the 113 pregnancies, antiviral therapy was initiated in 28 pregnancies (one low baseline HBV DNA woman and 27 high baseline HBV DNA women) at week 28 (median; range: 23–37) of pregnancy. In most cases (23/28, 82%), treatment was indicated for high viremia (median: 8.0 log IU/ml; range: 5.6–8.7 log IU/ml) to reduce the risk of mother-to-child transmission, while five women (5/42, 18%) initiated treatment for both high viremia and elevated ALT (63–264 U/l). Of those women who initiated antiviral therapy, over half (16/28, 57%) discontinued treatment by postpartum week 1 while 43% (12/28) continued treatment. Women in both groups—two women who continued treatment during postpartum and three women who discontinued treatment at delivery—had subsequent flares in ALT (180–1429 U/l) within the first 3 months postpartum.

Predictors for flares

On univariate analysis to estimate odds ratios for flares in HBV DNA or ALT, age, HBeAg positivity, baseline HBV DNA, baseline ALT, gravida, and parity were not found to be significant predictors in univariate or multivariate analyses (Table 3).

DISCUSSION

In this study, we retrospectively evaluated HBV DNA and ALT changes during pregnancy and postpartum in CHB women with high and low baseline HBV DNA. Previous studies have focused on identifying factors influencing mother-to-child transmission in HBeAg-positive, highly viremic women (5,22,23). Less is known on the effects of pregnancy and postpartum on HBV activity, especially in women with low viremia or negative HBeAg status. One retrospective study of 24 HBeAg-positive and 14 HBeAg-negative pregnancies reported that HBV DNA increased during pregnancy and decreased postpartum (18), thereby supporting the hypothesis that HBV activity follows the immunosuppressive changes during pregnancy, which reverse after delivery. Another study of 29 pregnancies found increases in HBV DNA during pregnancy or early postpartum, but HBV DNA was highly variable (9). Effects on HBV DNA during postpartum are less clear, with studies showing significant increases in HBV DNA in HBeAg-negative women, large fluctuations in women with HBeAg-positive women (15,24,25), and no significant change in a prospective study of untreated, mostly HBeAg-negative pregnant women (2.3 vs. 2.7 log IU/ml, $P=0.066$) (26).

Here, we found 9% of untreated women had an increase in HBV DNA of ≥ 2 log IU/ml, mostly during late pregnancy, but also observed during the first 3 months partum. Most women who had increases in HBV DNA during pregnancy and were untreated during postpartum quickly returned to baseline levels. However, some women who remained untreated or discontinued therapy at delivery sustained HBV DNA levels lower than baseline for 3 months to 1 year after delivery (Figure 1). This suggests that immunological changes during pregnancy, rather than antiviral therapy itself, may stimulate immunoclearance, and would support the higher than expected rates of HBeAg seroconversion (12–17%) previously reported in CHB pregnant women (15,27).

Table 2. Onset and severity of flares during pregnancy and postpartum

	Baseline HBV DNA $\leq 2,000$ IU/ml ($n=45$)		Baseline HBV DNA $>2,000$ IU/ml ($n=68$)	
	Pregnancy	Postpartum ^a	Pregnancy	Postpartum ^a
Flare in HBV DNA	9.4% (3/32)	8.7% (2/23)	8.6% (5/58)	0% (0/25)
Peak HBV DNA in women with flare ^b	6.0 \pm 1.4	6.5 \pm 1.5	7.1 \pm 0.7	—
Δ HBV DNA in women with flare ^c	3.5 (2.1–5.2)	4.4 (3.2–5.7)	2.9 (2.1–3.6)	—
HBV DNA flare onset week ^c	27 (4–36)	9 (7–11)	28 (10–29)	—
T1	33.3%	—	20.0%	—
T2	0.0%	—	20.0%	—
T3	6.7%	—	60.0%	—
PPM 1	—	50.0%	—	—
PPM 2	—	50.0%	—	—
Peak HBV DNA in women without flare ^b	2.1 \pm 1.0	2.3 \pm 1.1	6.5 \pm 1.9	4.8 \pm 2.2
Flare in ALT	4.6% (2/44)	7.1% (2/28)	7.4% (5/68)	13.0% (3/23)
Peak ALT in women with flare ^c	369 (301–437)	142 (109–175)	384 (213–2522)	193 (99–363)
ALT flare onset ^c	24 (20–27)	9 (7–11)	31 (10–35)	9 (3–9)
T1	0.0%	—	20.0%	—
T2	50.0%	—	20.0%	—
T3	50.0%	—	60.0%	—
PPM 1	—	0.0%	—	33.3%
PPM 2	—	50.0%	—	6.7%
PPM 3	—	50.0%	—	0.0%
Peak ALT in women without flare ^c	30 (12–85)	33 (14–113)	42 (8–153)	46 (19–106)
Flare in HBV DNA and ALT	3.1% (1/32)	4.6% (1/22)	6.9% (4/58)	0% (0/22)
Peak HBV DNA in women with flare ^b	7.0	7.6	7.1 \pm 0.8	—
Δ HBV DNA in women with flare ^c	5.2	5.7	3.1 (2.4–3.6)	—
Peak ALT in women with flare ^c	301	175	355 (213–390)	—

ALT, alanine aminotransferase; HBV, hepatitis B virus.

Units of HBV DNA in log IU/ml; ALT in U/l.

^aWomen who had not resolved flares during pregnancy were excluded in analysis of postpartum flares.

^bMean \pm s.d.

^cMedian (range).

In the setting of pregnancy in general, ALT has been reported to be lower than in non-pregnancy settings with low rates of ALT flare during this period (17,18,24). ALT flares during postpartum have been more commonly described, but reported rates are highly variable (2–62%), as a result of differences in definitions for flare, patient baseline characteristics, and antiviral therapy (5,16–18,20,22–24,26). Most of the current knowledge on postpartum ALT flares derives from large, prospective studies in Asia of HBeAg-positive, highly viremic women (5,22,23,28) and a few smaller, prospective studies (17,20,26). We found moderate rates of ALT flare during postpartum and pregnancy (6–10%) in HBeAg-positive and HBeAg-negative women. Flares were generally asymptomatic, although one was associated with hepatic decompensation. Although it is generally reported that ALT levels begin to rise during late third trimester or early postpartum (7,19,24),

about half of ALT flares that we observed during pregnancy were first detected during second trimester or earlier. Clinicians should be aware that flares may begin as early as second trimester, so that they can make informed decisions on closer monitoring or initiation of antiviral therapy in a time-appropriate manner.

Flares upon treatment withdrawal are also known to occur, especially in HBeAg-positive patients (29). Although not the primary end point of our study, of the women who initiated therapy during pregnancy and discontinued treatment within a week of delivery, 19% (3/16) subsequently flared. This falls within the range of reported rates of ALT flare in women with early postpartum treatment cessation (19–62%) (5,18,20). It remains unclear as to whether the extension of treatment during the postpartum period can prevent flare (20,30). In our study, extending treatment did not always prevent postpartum flares, as two women flared

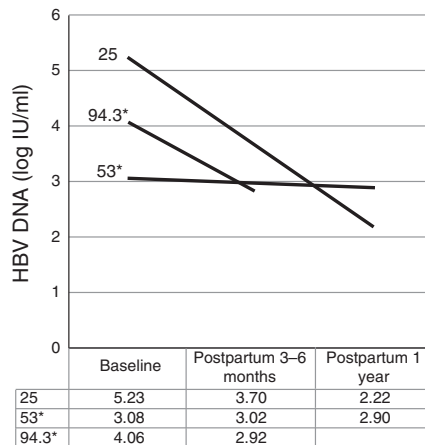


Figure 1. HBV DNA in women who had ≥ 2 log IU/ml increases in HBV DNA during pregnancy. Subject 25 remained untreated during pregnancy, and subjects 53 and 94.3 initiated treatment during pregnancy and stopped treatment at delivery. HBV, hepatitis B virus.

Table 3. Predictors for flares in HBV DNA or ALT during pregnancy or postpartum in high and low baseline HBV DNA women

	Univariate		Multivariate	
	OR (95%)	P value	aOR (95%)	P value
Age	1.06 (0.94–1.19)	0.36	1.09 (0.94–1.25)	0.24
HBeAg+	0.63 (0.18–2.20)	0.47	0.87 (0.09–8.21)	0.90
Baseline HBV DNA	0.91 (0.73–1.14)	0.42	0.92 (0.60–1.42)	0.72
Baseline ALT	1.01 (1.00–1.02)	0.13	1.01 (1.00–1.02)	0.19
Gravida	0.94 (0.65–1.36)	0.75		
Parity	0.77 (0.39–1.49)	0.43	0.58 (0.24–1.44)	0.24

ALT, alanine aminotransferase; aOR, adjusted odds ratio; HBV, hepatitis B virus; OR, odds ratio.

while on treatment, thus underscoring the need for close monitoring in both patients on and off treatment.

AASLD guidelines recommend antiviral therapy for pregnant women with HBV DNA $>200,000$ IU/ml, even in the absence of clinical symptoms, in order to reduce mother-to-child transmission, and monitoring for ALT flares every 3 months for 6 months when antiviral therapy is discontinued (31). However, there is no consensus on the management of HBV in women with HBV DNA $\leq 200,000$ IU/ml, women with active hepatic inflammation or advanced fibrosis, or who become pregnant while on therapy (31,32). Whether or not these women begin antiviral therapy, however, they should be closely monitored during pregnancy and early postpartum for increases in ALT and HBV, as we found ALT and HBV flares could occur in both treated and untreated women.

There are a number of limitations to this study. Increases in ALT and HBV DNA may have been due to inherent variations in

patients, rather than the effects of pregnancy though frequency and/or severity of spontaneous flares may not be as common in the general setting. There may be sampling bias with the referral of patients to the sites included in this study. Owing to late referral, not all patients had data prior to pregnancy for more robust baseline comparison. In addition, many patients did not have sufficient postpartum follow-up data. Most patients were also Asian and results may not be generalizable to non-Asian women with CHB. Finally, this study was not population-based, and therefore does not necessarily represent the general population of HBV-infected pregnant women. However, it was still multicenter, including patients from different practice types and different regions of the US.

CONCLUSION

In conclusion, significant HBV DNA and ALT flares can occur during late pregnancy and early postpartum in women with CHB. Although flares are mostly asymptomatic and resolve spontaneously, some can be severe and result in symptomatic hepatic decompensation. HBV-infected women should therefore be closely monitored during pregnancy and early postpartum. Further investigation is needed to help clinicians identify factors associated with flare and to manage CHB during pregnancy. HBV DNA and ALT monitoring every 4–6 weeks during first and second trimesters, as well as every 4 weeks during third trimester, and at postpartum months 3 and 6 should be considered in women with CHB.

CONFLICT OF INTEREST

Guarantor of article: Mindie H. Nguyen, MD, MAS.

Specific author contributions: Christine Chang: study design, data collection, data analysis and interpretation, and drafting of the manuscript. Natali Aziz: data collection, data interpretation, and review of the manuscript. Mugilan Poongkunran: data collection, data interpretation, and review of the manuscript. Asad Javaid: data collection, data interpretation, and review of the manuscript. Huy Trinh: data collection, data interpretation, and review of the manuscript. Daryl Lau: data collection, data interpretation, and critical review of the manuscript. Mindie Nguyen: concept development, study design, data collection, data analysis and interpretation, and critical revision of the manuscript. All authors identified above have critically reviewed the paper and approved the final version of this paper, including the authorship statement.

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advisory board of Gilead Sciences, Bristol-Myers Squibb, Roche Laboratories, Alnylam Pharmaceuticals, Intercept Pharmaceuticals, and Janssen Pharmaceuticals.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Vertical transmission is the primary mode of transmission for hepatitis B virus (HBV) in most endemic areas.
- ✓ Optimal use of antiviral therapy in pregnant women with HBV infection remains controversial.
- ✓ Reactivation of HBV can occur during pregnancy and postpartum but frequency, severity, and monitoring during pregnancy remain unclear.

WHAT IS NEW HERE

- ✓ Reactivation or "flares" with HBV DNA and/or alanine aminotransferase (ALT) elevation during pregnancy and during postpartum is common (up to 9% and 10%, respectively) and can be severe.
- ✓ Timing of flares can be variable but more common during second and third trimester (vs. first trimester) and during early postpartum period (first 3 months).
- ✓ As a result, more frequent monitoring with HBV DNA and ALT measurement during late pregnancy and early postpartum may help identify women at risk for severe hepatitis flares or higher rate of mother-to-child HBV transmission.

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