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Clinical course of hepatitis B virus infection during pregnancy

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SUMMARY

Background
For women with hepatitis B virus (HBV) infection, little is known about the natural progression of the disease during pregnancy or its impact on pregnancy outcomes.

Objectives
To investigate the natural progression of HBV infection during pregnancy or its impact on pregnancy outcomes.

Methods
In this retrospective cohort study, we reviewed medical records of all patients who were pregnant and presented with HBsAg-positivity between 2000 and 2008 at a community gastroenterology practice and a university hepatology clinic. Maternal characteristics were analysed according to maternal and perinatal outcomes.

Results
A total of 29 cases with at least 2 measurements of either HBV DNA or alanine aminotransferase (ALT) levels were included. Older age was the only predictor of a trend towards higher risk of an adverse clinical outcome [OR = 1.21 (0.97–1.51), $P = 0.089$], defined as either a negative foetal outcome (premature delivery, spontaneous abortion), or a negative maternal outcomes (gestational diabetes mellitus, pre-eclampsia, hepatic flare, liver failure). This trend for age remained even after adjusting for baseline ALT. Baseline serum HBV DNA, ALT, hepatitis B e antigen status, gravida and parity were not significant predictors for adverse clinical outcomes. Four patients developed liver failure.

Conclusions
Maternal and neonatal outcomes are highly variable in this clinic-based patient cohort. Severe complications due to HBV infection can occur during pregnancy in previously asymptomatic patients. It is unclear how generalizable the results observed in this cohort would be to the general population; therefore, further studies are needed to identify reliable predictors for significant adverse outcomes and until more data are available, pregnant patients with HBV infection should be monitored with periodic serum HBV DNA and ALT levels.

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INTRODUCTION

Chronic hepatitis B virus (HBV) infection can lead to serious liver disease, including cirrhosis, hepatocellular carcinoma (HCC) and/or liver failure.[1, 2] It is estimated that nearly 350 million people worldwide are chronically infected with HBV and in regions where HBV is endemic, such as China and Southeast Asia, the prevalence of HBV infection among women of child-bearing age may be as high as 10–20%.[3] This prevalence in pregnant women who are HBV carriers is of particular concern as vertical transmission from an infected mother to her newborn child remains the predominant mode of infection in such areas. Despite the availability of highly effective passive-active immunoprophylaxis for the prevention of vertical transmission of HBV using hepatitis B immune globulin (HBIG) and hepatitis B vaccine, high maternal serum HBV deoxyribonucleic acid (DNA) levels have been associated with failure of immunoprophylaxis.[4–6] In such cases, clinicians might consider administering anti-viral therapy during the third trimester of pregnancy to reduce HBV DNA levels, although data supporting this approach are still limited.[4–8] In addition to lowering or eliminating the probability of an infected mother passing HBV to her newborn, anti-viral therapy in pregnant women may protect maternal health from possible HBV-associated hepatitis flares or reactivation including progression to hepatic decompensation,[9] although anti-viral treatment is generally recommended to be postponed for mild disease until after delivery.[10]

A number of physiological changes can occur during the normal course of pregnancy that may affect the course of chronic hepatitis B in infected women.[4, 11–13] For example, even though foetal antigens are allogeneic to the mother's immune system and should theoretically elicit an immune response, they fail to do so, which may be explained by modulation of the maternal immune system as part of an adaptation necessary for successful foetal development. It is possible that these changes in the immune system during pregnancy might allow greater viral replication in those with chronic hepatitis B.[13] Pregnant women also have increased levels of oestrogen and progesterone and these hormones can have immunosuppressive effects that may enhance HBV replication as well.[14] On the other hand, oestrogen has been shown to suppress HBV expression in male athymic mice.[15] The high level of sex steroids may also cause changes in the synthetic, metabolic and excretory functions of the liver.[16] Currently, little is known of the impact of pregnancy on the natural course and progression of chronic HBV infection or, conversely, how HBV infection impacts pregnancy.

The goal of this study was to examine the clinical course of 29 pregnant women diagnosed with HBV infection who were seen by gastroenterologists in a community practice or at a university hepatology clinic in Northern California.

MATERIALS AND METHODS

Study design and subjects

A retrospective cohort study was performed of all patients diagnosed with HBV infection who became pregnant or presented with hepatitis B during pregnancy between 2000 and 2008 at a community-based gastroenterology practice in San Jose and at the Hepatology Clinic at Stanford University Medical Center. Patients met inclusion criteria if they had at least two data points available including either serum HBV DNA or alanine aminotransferase (ALT) levels before or during their pregnancy. To abstract patient data, a case report form was created and included various baseline demographic characteristics such as maternal age, parity, gravida, ethnicity, family history of liver disease or HCC, social history (alcohol use and smoking), risk factors for HBV and various co-morbidities. HBV serology, including hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) status, was also recorded. Patients who tested positive for hepatitis C virus, hepatitis D virus or human immunodeficiency virus were excluded from the study. Serum HBV DNA levels and liver biochemical tests were noted at baseline before pregnancy, during pregnancy and post-partum for each patient. The baseline parameter was defined as the most recent HBV DNA or ALT level available in the medical record prior to the start of the pregnancy. Finally, foetal and maternal outcomes of pregnancy, any complications that occurred, and any treatment with nucleos(t)ide analogues were also recorded. Details of the four cases with severe maternal and/or foetal adverse outcomes were also described. This protocol was approved by the Administrative Panels on Human Subjects in Medical Research at Stanford University.

Statistical analysis

Information on demographic characteristics, liver biochemical tests and HBV DNA levels were collected and analysed according to pregnancy outcomes. Subjects were categorized as having either a benign clinical outcome or an adverse clinical outcome. Adverse clinical outcomes included a negative birth outcome (premature delivery, spontaneous abortion/miscarriage) or complications experienced during pregnancy, whether non-liver related [gestational diabetes mellitus, pre-eclampsia, HELLP (haemolytic anaemia, elevated liver enzymes, and low platelet count) syndrome, etc] or liver-related (hepatic flare, liver failure). Benign clinical outcome was assigned if there were no known complications to both foetus/infants and mothers.

Chi-squared (χ^2) statistics were used to evaluate categorical variables, while a student *t*-test was applied to continuous variables. A *P*-value of less than 0.05 was considered significant. Logistic regression was used to determine odds ratios (OR) and 95% confidence intervals (CI) for adverse clinical outcome as it related to age, ethnicity, gravida, parity, HBeAg status, baseline HBV DNA level and baseline ALT levels. All statistical analysis was performed using Stata version 10.0 (Stata Corporation, College Station, TX, USA).

RESULTS

In total, 39 subjects were identified via computer query using combined ICD-9 codes for HBV infection and for pregnancy and their medical charts were reviewed. Eight subjects were excluded because only single determinations of serum HBV DNA or ALT levels were available and two other subjects whose pregnancies were terminated early in the first trimester were also excluded. A total of 29 subjects were included in the final analysis. None of the study patients had prior history of hepatic decompensation. Baseline characteristics of study subjects are shown in Table 1a and 1b. Although patients who had an adverse clinical outcome appeared more likely to be older (mean age, 34 ± 4.7 years) than patients who had a benign clinical outcome (mean age,

Table 1a. Demographic characteristics of all patients and by clinical outcomes

Patient characteristics	All patients* (*n* = 29)	Benign clinical outcome (*n* = 16)	Adverse clinical outcome (*n* = 7)	*P*-value
Mean maternal age	30.3 ± 4.6	30.1 ± 4.7	34.1 ± 4.7	0.08
Gravida				
1	17 (59%)	9 (56%)	3 (43%)	0.25
≥2	12 (41%)	7 (44%)	4 (57%)	
Parity				
0	19 (66%)	10 (63%)	5 (71%)	0.20
≥1	10 (34%)	6 (37%)	2 (29%)	
Ethnicity				
Vietnamese	12 (41%)	6 (38%)	4 (57%)	0.47
Chinese	8 (28%)	4 (25%)	3 (43%)	
Filipino	4 (14%)	4 (25%)	0	
Korean	2 (7%)	1 (6%)	0	
South Indian	1 (3%)	1 (6%)	0	
Thai	1 (3%)	0	0	
Samoan	1 (3%)	0	0	
Family history				
Liver disease	1 (3%)	1 (6%)	0	0.50
Liver cancer	2 (7%)	0	1 (14%)	0.12
Habits				
Smoking	1 (3%)	0	0	–
Alcohol	0%	0	0	–
Co-morbid diseases				
Hypertension	2 (7%)	1 (6%)	1 (14%)	0.53
Diabetes mellitus	2 (7%)	1 (6%)	1 (14%)	0.53

* Clinical outcomes were unknown in six patients.

Table 1b. Mean baseline lab values for all patients and by clinical outcomes

Laboratory tests	All patients* (n = 29)	Benign clinical outcome (n = 16)	Adverse clinical outcome (n = 7)	P-value
HBeAg-positive	13 (45%)	7 (44%)	2 (29%)	0.49
ALT (U/L)	(n = 17)	(n = 11)	(n = 4)	0.37
	31 ± 16	38 ± 26	26 ± 9	
HBV DNA (IU/mL)	(n = 17)	(n = 12)	(n = 3)	0.92
	$1.9 \times 10^7 \pm 4.0 \times 10^7$	$1.5 \times 10^7 \pm 3.5 \times 10^7$	$1.3 \times 10^7 \pm 2.2 \times 10^7$	
Alkaline phosphatase (U/L)	(n = 16)	(n = 11)	(n = 3)	0.98
	53 ± 15	60 ± 26	60 ± 26	
Albumin (g/dL)	(n = 16)	(n = 11)	(n = 3)	0.99
	4.2 ± 0.28	4.3 ± 0.33	4.2 ± 0.46	
Total bilirubin (mg/dL)	(n = 16)	(n = 11)	(n = 3)	0.20
	0.66 ± 0.28	0.61 ± 0.30	0.87 ± 0.23	
Platelet count ($x10^9$/L)	(n = 10)	(n = 7)	(n = 2)	0.37
	233 ± 74	254 ± 76	195 ± 76	

* Clinical outcomes were unknown in six patients.

30 ± 4.7 years), this difference was not statistically significant (P = 0.08). There were no other differences in terms of baseline characteristics between the benign and adverse outcome groups.

Table 2a shows serum HBV DNA and ALT levels during pregnancy for 18 patients whose baseline data were known. Table 2b shows results for the remaining 11 patients who did not have any baseline data. ALT rose above 40 U/L in approximately half (48%) of all patients at some time during pregnancy. Among those who had baseline data, ALT increased in 59% of patients during pregnancy, but actually decreased or

Table 2a. Changes in HBV DNA and ALT levels for patients whose baseline data were available (n = 18)

Patient (n = 18)	HBeAg Status	Baseline HBV DNA (log_{10}IU/mL)	Maximum HBV DNA during pregnancy (log_{10}IU/mL)	Δ (log_{10}IU/mL)	Maximum DNA/ Baseline DNA ratio	Baseline ALT (U/L)	Maximum ALT during pregnancy (U/L)	Δ (In U/L)	Maximum ALT/ Baseline ALT ratio
1	+	8.09	7.68	−0.41	0.95	23	40	+17	1.74
2	−	3.3	2.88	−0.42	0.87	22	14	−8	0.64
3	−	4.04	4.58	+0.54	1.13	18	35	+17	1.94
4	+	N/A	N/A	N/A	N/A	64	42	−22	0.66
5	+	8.07	8.18	+0.11	1.01	33	70	+37	2.12
6	−	7.31	6.24	−1.07	0.85	59	87	+28	1.47
7	+	3.38	3	−0.38	0.89	13	12	−1	0.92
8	+	3.8	2.7	−1.1	0.71	15	15	0	1
9	−	3.58	4.39	+0.81	1.23	19	13	−6	0.68
10	−	5.28	6.28	+1.0	1.19	54	81	+27	1.5
11	−	<1.08	6.97	+6.97	6.45	38	295	+257	7.76
12	+	>7.58	>7.58	–	1	27	75	+48	2.78
13	−	N/A	N/A	N/A	N/A	19	1,540	+1,521	0.28
14	+	1.56	5.86	+4.3	3.76	18	39	+21	2.17
15	+	>7.58	>7.58	–	1	42	48	+6	1.14
16	−	1.64	<1.08	−1.64	0.66	36	29	−7	0.81
17	−	3.6	2.89	−0.71	0.80	22	17	−5	0.77
18	−	<1.08	6.82	+6.82	6.31	N/A	N/A	N/A	N/A

Table 2b. Maximum HBV DNA and ALT levels for patients whose baseline data were not available (n = 11)

Patient (n = 11)	HBeAg status	Maximum HBV DNA ($\log_{10}$IU/mL)	Maximum ALT (U/L)
19	+	6.34	41
20	+	6.63	44
21	−	<1.08	29
22	−	4.58	11
23	−	2.08	70
24	−	3.38	65
25	+	7.69	261
26	+	7.98	586
27	−	6.78	2522
28	+	6.28	32
29	−	2.21	10

remained the same in 41% of patients. HBV DNA increased during pregnancy in 44% of subjects, but decreased in 56%. In addition, increases in ALT were not necessarily accompanied by concurrent increases in HBV DNA. HBeAg-positive patients had mean HBV DNA levels during pregnancy of approximately 2.6 $\log_{10}$ IU/mL greater than that of HBeAg-negative patients.

Figures 1a and 2a show the changes in ALT over time of all patients, with each different coloured line representing one patient. Likewise, Figures 1b and 2b show the changes in serum HBV DNA over time of all patients. The results are separated into 'treated during pregnancy' and 'untreated during pregnancy' groups because the treated subjects in Figure 2a and 2b were expected to have decreases in their HBV DNA and ALT levels whenever they began treatment. Of the nine patients who received anti-viral therapy during pregnancy, one patient had started anti-HBV therapy (lamivudine 100 mg daily) prior to conception. This patient immediately halted treatment early in the 1st trimester when she realized she was pregnant and later delivered a full-term baby with no complications. The remaining eight patients began anti-HBV therapy during the third trimester. Six of these eight patients received lamivudine 100 mg daily and two patients received telbivudine 600 mg daily. The indication for anti-viral therapy were for treatment of maternal hepatitis flares and/or hepatic failures in three patients (further described below) and for prevention of vertical transmission in five patients whose HBV DNA level were very high during their second and/or third trimester (maximum HBV DNA PCR = 6 000 000 IU/mL to 150 200 000 IU/mL). Three patients discontinued their therapy (with lamivudine) at delivery. None of the patients who had hepatitis flares or hepatic failure discontinued therapy at delivery.

Figures 3 and 4 show foetal birth outcomes and maternal complications during pregnancy.

In univariate analysis, there were no significant predictors (baseline HBV DNA, ALT, alkaline phosphatase, albumin, total bilirubin, platelet count, HBeAg status, gravida, or parity) for adverse clinical outcome. Older age was the only predictor, with a trend towards higher risk of adverse clinical outcome [OR = 1.21 (0.97–1.51), P = 0.089]. Following adjustments for baseline ALT, the trend for increased risk of adverse outcome with older age remained (OR = 1.45, P = 0.082).

Cases with severe adverse outcomes

During the study, there were four cases in which reactivation of hepatitis B during pregnancy put patients at risk for or caused liver failure. In the first case (patient #11 in tables and figures), a 39-year-old Chinese woman (G1, P0) with a history of chronic HBV infection that had been quiescent with persistently normal ALT and undetectable HBV DNA levels for at least 2 years prior to the pregnancy presented in the third trimester with gestational diabetes, elevated alpha-fetoprotein to several hundred ng/mL, thrombocytopenia and hepatic flare characterized by an ALT level of 295 U/L and rapidly rising HBV DNA level up to 9.4×10^6 IU/mL. Due to the risk of hepatic decompensation, she was treated with lamivudine 100 mg once daily. She then went into pre-term labour and gave birth via caesarean section to healthy twin boys, after which she was switched to telbivudine 600 mg daily. Telbivudine was chosen as the patient declined to use any contraception and telbivudine is not only an agent with a lower risk of viral resistance than lamivudine but also a category B drug. After 5 months of post-partum therapy, the patient achieved complete viral suppression with a serum HBV DNA level <100 IU/mL.

The second case (patient #26) was a 27-year-old Vietnamese woman (G1, P0) who first noticed that she had dark urine and was jaundiced during the eighth month of her pregnancy. Upon admission to the hospital, she was noted to have acute liver injury manifested by a peak total bilirubin value of

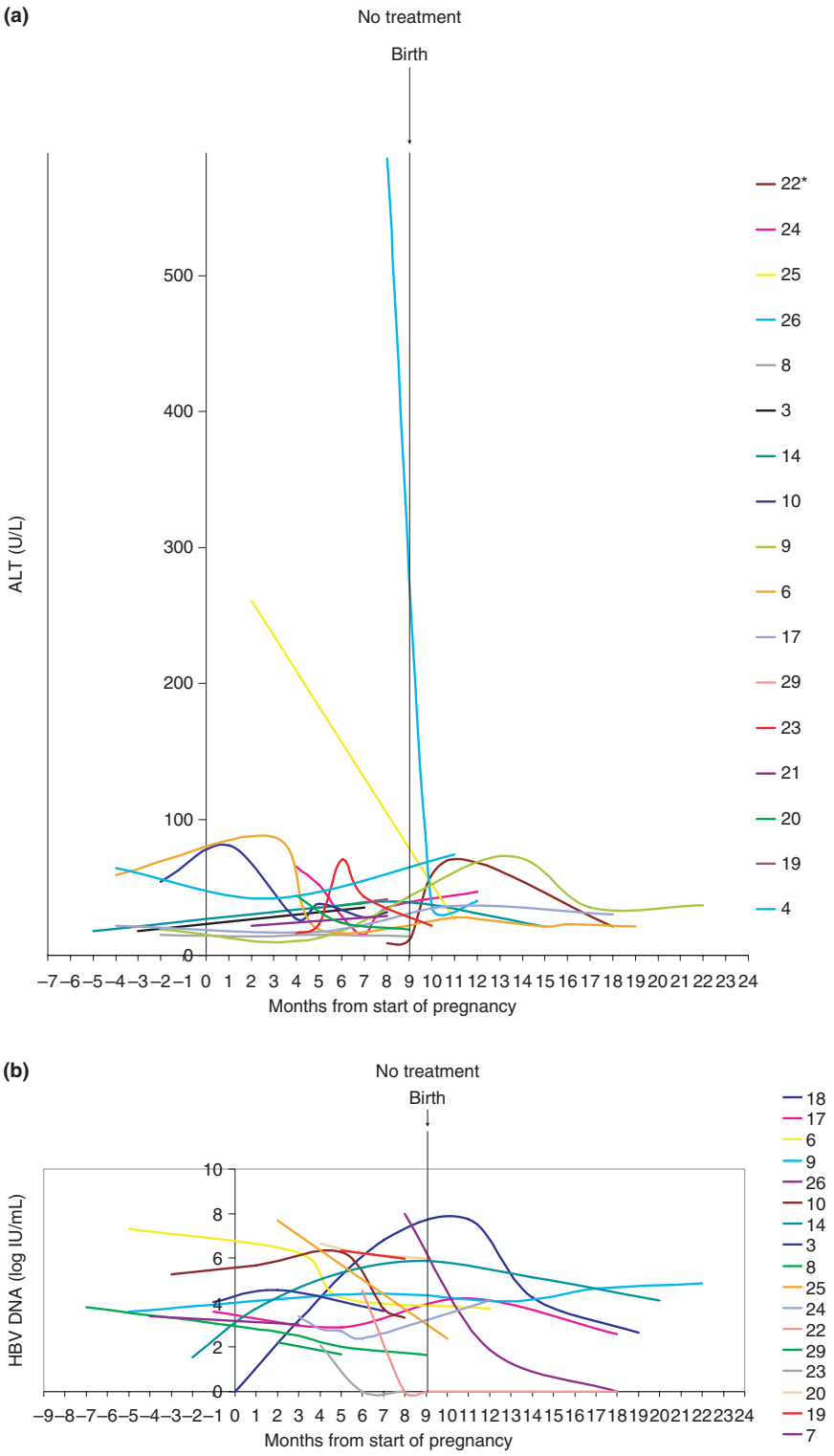

Figure 1. (a) Changes in ALT levels of patients who were not treated for hepatitis B during pregnancy (n = 17). *Each colour and number denotes an individual patient. (b) Changes in HBV DNA levels of patients who were not treated for hepatitis B during pregnancy (n = 17). * Each colour and number denotes an individual patient.

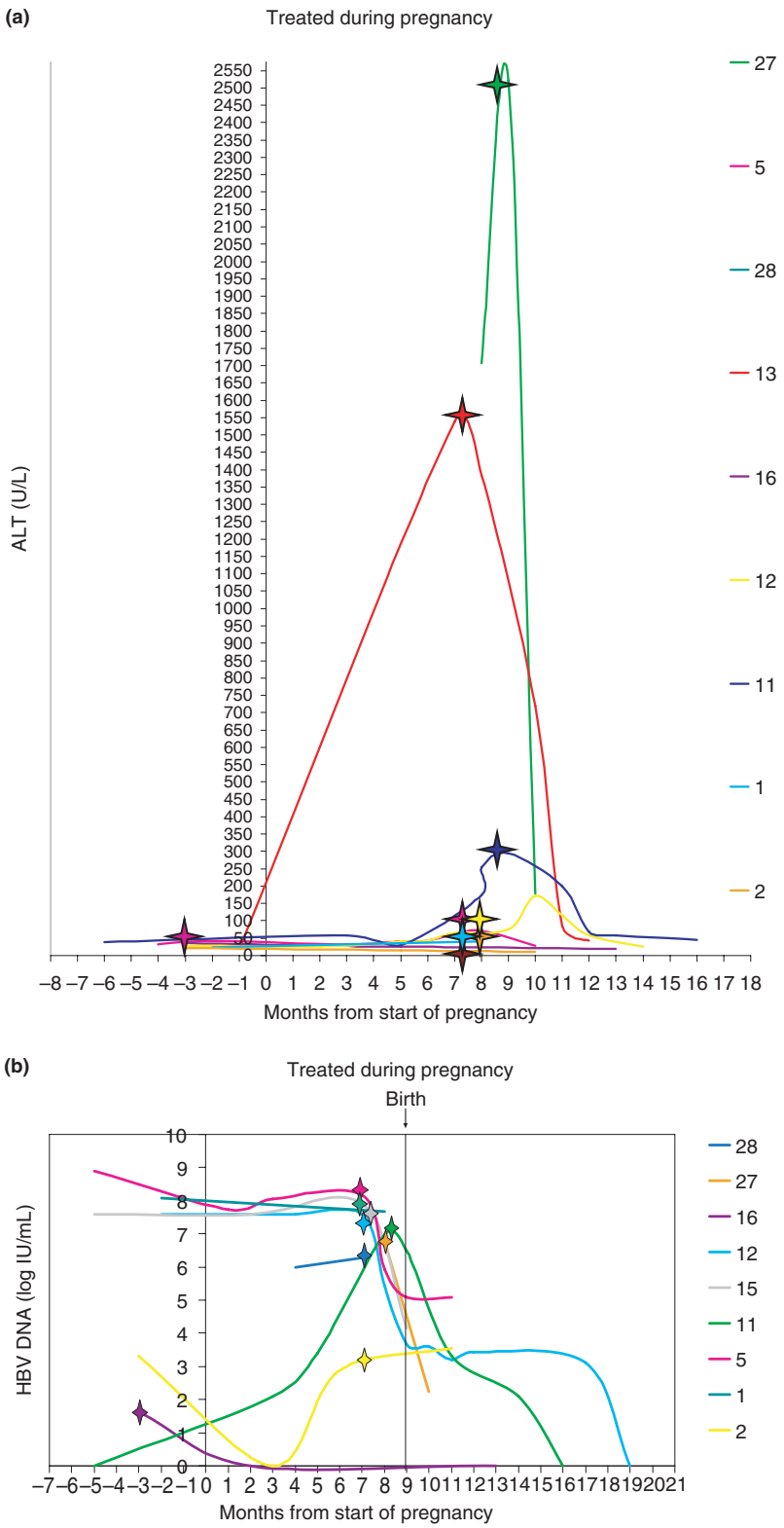

Figure 2. (a) Changes in ALT levels of patients who were treated for hepatitis B during pregnancy (n = 9). ✦ Indicates point when treatment was started: * Each colour and number denotes an individual patient. (b) Changes in HBV DNA levels of patients who were treated for hepatitis B during pregnancy (n = 9). ✦ Indicates point when treatment was started: * Each colour and number denotes an individual patient

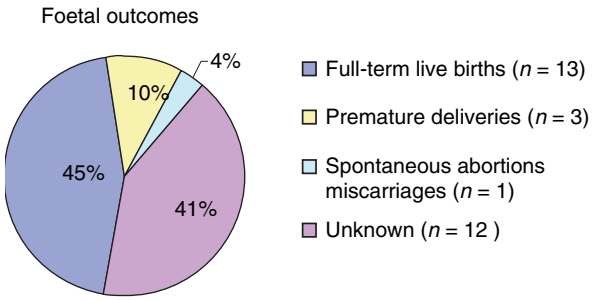

Figure 3. Foetal outcomes in mothers with HBV infection.

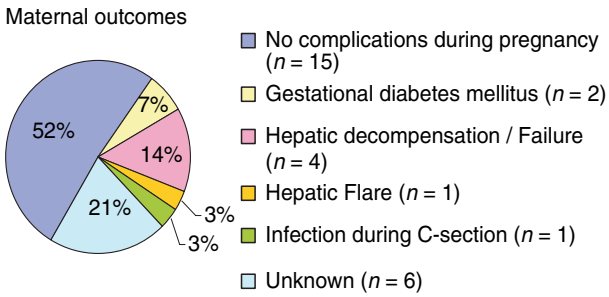

Figure 4. Outcomes of mothers with chronic hepatitis B infection.

12 mg/dL, international normalized ratio for prothrombin time (INR) of 2.6, and aspartate aminotransferase (AST) and ALT in the 500 to 600 U/L range. Serum HBV DNA level was 9.5×10^7 IU/mL, indicating active viral replication. The patient was also noted to have altered mental status and renal insufficiency with fluid overload. Emergency caesarean section was performed at 34 weeks without complication. She was treated post-partum with entecavir 0.5 mg daily and evaluated for liver transplantation. Post-partum liver function improved significantly and the patient was removed from the liver transplant list. At discharge, her ALT level had decreased to 29 U/L, with all other laboratory values nearing complete normalization.

The third case (patient #27) was a 34-year-old Vietnamese woman (G3, P2) who developed acute liver failure during pregnancy. Until the third trimester of her third pregnancy, the patient had a 5-year history of HBV infection without any clinical manifestations. However, she then developed jaundice and became easily fatigued during the third trimester of pregnancy. Laboratory tests revealed significant liver dysfunction, with a total bilirubin of 16 mg/dL, INR of 2.8, AST of 2700 U/L, and ALT of 2522 U/L. Consequently, she was treated with lamivudine 150 mg once daily. The patient later went into pre-term labour at 33 weeks and underwent an uneventful caesarean section of a viable female infant. One day after giving birth, however, she deteriorated clinically with the development of hepatic encephalopathy (stage I to stage II) with lethargy and asterixis. At that point, her serum HBV DNA level was 6 million IU/mL and she was switched to entecavir 0.5 mg once daily, with subsequent improvement in liver enzymes. At discharge, her tremors and mental confusion had completely resolved, although she still remained jaundiced.

The fourth case (patient #13) was a 38-year-old Vietnamese woman (G3, P0) with history of asymptomatic hepatitis B who was 22 weeks pregnant when she developed right upper quadrant pain and jaundice and was subsequently diagnosed with acute liver failure with hepatitis B and she was treated with lamivudine 100 mg per day. Despite this therapy, her hepatitis progressed and she developed hepatic encephalopathy, with increase in ALT to 1540 U/L and AST to 2014 U/L. Lack of foetal movement was then noted leading to the diagnosis of foetal demise and she underwent dilatation and evacuation. The patient's continuing acute liver failure was accompanied by hypoglycaemia, coagulopathy and pulmonary oedema requiring mechanical ventilation. She remained comatose and unresponsive and underwent liver transplantation 1 week later. Her anti-viral medication was transitioned to entecavir and her liver enzymes eventually returned to normal. She had ongoing psychosis and depression that were attributed to the loss of her child, the ensuing liver failure and liver transplantation and the hormonal and chemical changes that accompanied these dramatic events.

DISCUSSION

Little information is available regarding the natural history of chronic HBV infection during pregnancy or the impact of hepatitis B on outcomes of pregnancy. There are also few published studies of the effect of pregnancy on serum HBV DNA levels of women with chronic HBV infection. One such study by Soderstrom *et al.* retrospectively examined the alterations in HBV DNA levels measured in stored sera during and after

55 pregnancies in 33 HBsAg-positive mothers.[17] Increased serum HBV DNA levels by a mean of 0.4 $\log_{10}$ IU/mL were found in late in pregnancy or early post-partum, with concomitant increase in ALT levels. Another recent study by ter Borg *et al.* similarly reported an exacerbation of chronic hepatitis B in the post-partum period, which the authors defined as a three-time increase in ALT within 6 months after delivery.[18] However, the Soderstrom study and the ter Borg study were conducted at a Swedish hospital and a university hospital in the Netherlands respectively, where the ethnic make-up and clinical profile (e.g. HBV genotype) of European patients are much different from those of patients in the U.S. For example, among the urban pregnant population in the United States, the highest prevalence of HBsAg positivity occurs among Asian-American women (6%) followed by African-Americans (1%), Caucasians (0.6%) and Hispanics (0.14%).[19] Our study population mirrors the reported statistics of high HBV rates among Asian-Americans, with the majority of our patients being of Vietnamese descent (45%) followed by Chinese (26%), Filipino (13%), Korean (6.5%), Indian, Thai and Samoan (3% each).

In our study, we found that the levels of HBV DNA and ALT were highly variable (Figures 1 and 2). While HBV DNA levels seemed to rise in the third trimester and in the post-partum period in a few patients, the levels in most patients (except for those who experienced hepatic flare or decompensation) remained stable throughout the course of pregnancy.

Opinions regarding the impact of hepatitis B on perinatal outcome are currently mixed.[20–22] Prior studies have reported that the frequency of reproductive casualties (spontaneous abortion, stillbirth, and prematurity) was much higher in HBsAg-positive women (80%) than in seronegative women (44%), although it should be noted that these studies often included cases of acute hepatitis B.[20] A larger and more recent study conducted by Wong and colleagues compared 824 HBsAg-positive women with 6281 controls.[21] The investigators reported that the presence of HBsAg in pregnant women did not pose additional risk for the pregnancy or its outcome. However, this study only included cases with live single birth >500 g and >24 weeks gestation and excluded higher-risk women such as those with twin pregnancy, acute hepatitis and other non-liver related co-morbidities. This study focused on perinatal outcomes without mentioning of maternal outcomes and did not take into account effects of maternal HBV DNA or ALT levels at baseline or during pregnancy. Another study by Tse *et al.* found that HBsAg carrier status was associated with higher risk for gestational diabetes mellitus and antepartum haemorrhage,[22] but not for pre-term labour prior 34 weeks gestation, foetal intraventricular haemorrhage, pre-eclampsia, or prelabour rupture of membranes. Impact of maternal HBV viraemia, HBeAg status or ALT levels on perinatal outcomes were not examined in this study.

Our study is retrospective and not population-based. As patients in this study were referred to a community gastroenterology and hepatology clinic or to a tertiary referral liver centre, they do not necessarily represent pregnant women with HBV infection in the general population. In our community, most pregnant women with chronic HBV infection generally obtain prenatal care from their obstetricians and the status of their HBV infection is not monitored by their primary care physicians or hepatologists. Consequently, nearly one-third of all patients did not have pre-pregnancy (baseline) data available. In the two cases in which patients did progress to acute liver failure during pregnancy, baseline HBV DNA data were not obtained before pregnancy or the development of clinical complications. Furthermore, these two patients were not evaluated by gastroenterologists or hepatologists prior to their clinical decompensation. In addition, lack of follow-up with primary care physicians or primary gastroenterologist also resulted in a significant proportion of unknown maternal and foetal outcomes in our cohort.

In summary, the majority of patients with chronic HBV infection who become pregnant will probably exhibit variable but stable disease throughout the course of their pregnancy. However, for the few patients who do experience a reactivation or flare of hepatitis B in pregnancy, the consequences may be serious, including the risk of progressing to liver failure and adverse foetal outcomes. Current literature on HBV infection in pregnancy is limited and there are no reliable predictors for poor outcomes. Therefore, with the limited data currently available, our best recommendation would be to monitor pregnant HBsAg-positive patients more closely with serum HBV DNA and ALT levels every 3 months and more frequently towards the end of the third trimester and especially if there are any symptoms or laboratory manifestations of clinical deterioration.

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