

Lamivudine Therapy in the Treatment of Chronic Hepatitis B with Acute Exacerbation During Pregnancy

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We report a case of chronic hepatitis B carrier gravida who had acute exacerbation during pregnancy. She had been taking lamivudine 100 mg/qd for 17 months when hepatitis B virus (HBV) DNA in the YMDD region of the polymerase gene (YMDD motif) mutant was noted. After discontinuing lamivudine, she became pregnant. HBeAg became positive again and liver enzymes were elevated during the first trimester of pregnancy. She received the hepatoprotective agent silymarin 150 mg bid at 13⁺² gestational weeks. Serum aspartate aminotransferase (AST) dropped to 757 U/L at 15⁺⁰ gestational weeks, but serum alanine aminotransferase (ALT) flared up to 2,230 U/L and AST to 2,250 U/L at 17⁺¹ gestational weeks. Serum HBV-DNA test revealed serum HBV-DNA concentration of 7.31×10^8 copies/mL. Lamivudine 100 mg/qd and silymarin 150 mg/bid were initiated at 17⁺¹ gestational weeks. Liver function showed gradual decline to ALT 341 U/L and AST 91 U/L at 21⁺⁰ gestational weeks, while HBeAg(+) converted to (-) and anti-HBe(-) converted to (+). Further treatment with lamivudine 100 mg/qd continued for 3 months. Serum HBV-DNA concentrations decreased to 3.19×10^2 copies/mL at 36⁺⁶ gestational weeks. Spontaneous delivery of a male baby weighing 3314 g occurred at 38⁺³ gestational weeks. The neonatal physical check-up revealed no congenital anomalies, and fetal growth was within normal reference ranges, suggesting that lamivudine may be safely used in the treatment of chronic hepatitis B with acute exacerbation during the second trimester of pregnancy. [*J Chin Med Assoc* 2008;71(3):155–158]

Key Words: hepatitis B, lamivudine, pregnancy

Introduction

Lamivudine is a pyrimidine nucleoside originally developed as an antiretroviral drug. It is a cytidine analog that metabolizes intracellularly to lamivudine triphosphate, which inhibits hepatitis B DNA polymerase as well as human immunodeficiency virus (HIV) reverse transcriptase. Lamivudine is an effective monotherapy for the treatment of chronic hepatitis B, and in combination with other antiretroviral drugs for the treatment of HIV-1 infection. Lamivudine has high oral bioavailability and a relatively long plasma half-life (5–7 hours), which makes once-daily dosing feasible for patients with chronic hepatitis B.¹

Lamivudine has proved beneficial in patients with chronic hepatitis B, and the effectiveness of lamivudine in the treatment of chronic hepatitis B has been confirmed in delaying clinical progression in patients with chronic hepatitis B and advanced fibrosis or cirrhosis.^{2–4} But there are few reports on the treatment of chronic hepatitis B with acute exacerbation during pregnancy. Here, we report a case of chronic hepatitis B carrier gravida who was treated with lamivudine from 17⁺¹ gestational weeks and delivered a male baby weighing 3,314 g with good Apgar scores at 38⁺³ gestational weeks. The newborn did not have congenital anomalies, and the neonatal growth was within normal reference ranges.



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Case Report

This G2P1, 32-year-old, female was an HBV carrier. After the patient gave birth to her first baby, a physical check-up revealed serum alanine aminotransferase (ALT) of 571 U/L, aspartate aminotransferase (AST) of 165 U/L, HBsAg(+), HBeAg(+) and anti-HCV(-). Under the impression of chronic hepatitis B with acute exacerbation, she received a first course of lamivudine therapy 100 mg/qd for 17 months. At the end of the first course of lamivudine therapy, HBeAg seroconversion went from positive to negative, but serum ALT and AST levels were 3–4 times normal. Under the clinical impression of YMDD motif mutation of the HBV polymerase gene, the patient stopped lamivudine therapy.

After discontinuation of lamivudine, she became pregnant. HBeAg became positive again. The serum liver enzyme ALT was as high as 1,570 U/L at 13⁺¹ gestational weeks. She began receiving the hepatoprotective agent silymarin, 150 mg bid, at 13⁺² gestational weeks. The serum liver enzyme AST remained at 757 U/L at 15⁺⁰ gestational weeks, but flared up to ALT 2,230 U/L and AST 2,250 U/L at 17⁺¹ gestational weeks (Figure 1). The measurement of serum HBV DNA during the second course of lamivudine treatment was performed by a quantitative PCR assay (Amplicor™ HBV monitor test; Roche Diagnostics).⁵ HBeAg was positive, and the HBV-DNA test revealed

serum HBV-DNA of 7.31×10^8 copies/mL at 17⁺¹ gestational weeks. Total serum bilirubin was 0.7 mg/mL and international normalized ratio at the time was 0.93. A second course of lamivudine 100 mg/qd and silymarin 150 mg bid was initiated. At 21⁺⁰ gestational weeks, serum liver enzymes showed a gradual decline to ALT 341 U/L and AST 91 U/L, while HBeAg(+) converted to (-) and anti-HBe(-) converted to (+). Further treatment with lamivudine 100 mg/qd continued for 3 months. Serum HBV-DNA decreased to 3.19×10^2 copies/mL at 36⁺⁶ gestational weeks. The patient experienced pruritic urticarial papules and plaques of pregnancy (PUPPP) at 37⁺⁶ gestational weeks and was given prednisolone 5 mg/qd for 7 days, and the PUPPP lesions subsided. Hepatitis B marker was re-checked and revealed HBsAg(+), HBeAg(-) and anti-HBeAb(+). International normalized ratio was 0.99 and total bilirubin was 0.4 mg/mL. Spontaneous delivery of a male baby weighing 3,314 g occurred at 38⁺³ gestational weeks with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. The mother experienced no lactic acidosis throughout the whole course of pregnancy.

The neonatal physical check-up revealed no congenital anomalies, and fetal growth was within normal reference ranges. Passive immunization with hepatitis B immune globulin 0.5 mL was injected immediately after delivery. The serum liver enzymes of the gravida were ALT 138 U/L and AST 40 U/L 2 months

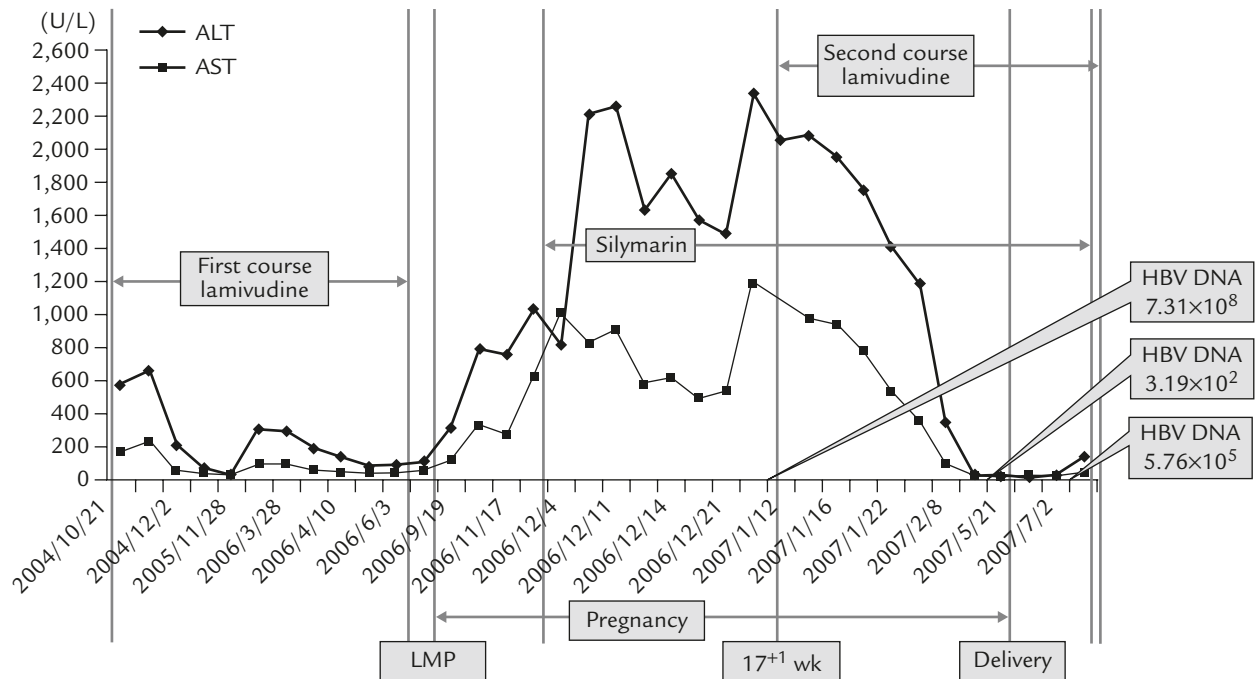


Figure 1. Clinical course of serum liver enzyme and HBV DNA profiles of the gravida complicated with chronic hepatitis B with acute exacerbation. HBV = hepatitis B virus; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

postpartum. But the HBV-DNA test revealed increased serum HBV-DNA of 5.76×10^5 copies/mL, and was positive for YMDD mutation.

Discussion

Using lamivudine for the treatment of a hepatitis B carrier with chronic exacerbation during the second trimester of pregnancy showed promising results. The liver enzymes decreased, and the newborn was free of teratogenic effects. In another report, no congenital anomalies were found in a large cohort of HIV-1-infected women who received antiretroviral therapy during pregnancy.⁶ The risk of an adverse outcome due to lamivudine treatment during pregnancy was not associated with the use of antiretroviral regimens overall.⁷

The nucleoside reverse-transcriptase inhibitors are generally well tolerated across the placenta. These agents have not been shown to be teratogenic in animals in concentrations similar to those used in humans. The rate of birth defects in more than 400 women exposed to zidovudine or lamivudine during the first trimester of pregnancy as reported to the Antiretroviral Pregnancy Registry was no higher than the rate of birth defects of women who were exposed to similar drugs after the first trimester as reported in the Metropolitan Atlanta Congenital Defects Program of the Centers for Disease Control and Prevention.⁸ Lamivudine is helpful in preventing maternal-infant HBV transmission and may reduce the complications of HBV-infected patients who become pregnant.⁹

Nucleoside reverse-transcriptase inhibitors that bind to mitochondrial DNA polymerase gamma can cause mitochondrial dysfunction, which may manifest as myopathy, cardiomyopathy, neuropathy, lactic acidosis, or fatty liver.⁸ Toxic effects of long-term therapy with nucleoside reverse-transcriptase inhibitors may be enhanced in women who become pregnant. Three deaths and additional cases of lactic acidosis and hepatic failure have been noted among pregnant women who began receiving stavudine and didanosine along with other drugs before pregnancy.⁸ Clinical findings are similar to those in acute fatty liver of pregnancy, a syndrome that is more frequent among women with heterozygous defects of mitochondrial fatty-acid metabolism who are carrying fetuses that are homozygous for the same defect.⁸

The major limitation of lamivudine treatment is the high rate of viral resistance related to mutations in the YMDD motif of the HBV polymerase gene.

The emergence of lamivudine-resistant mutants is usually associated with a breakthrough of hepatitis, with moderately increased levels of serum HBV-DNA and ALT, although these levels may be lower than the baseline (pretreatment) for several months.¹⁰ The first manifestation of antiviral resistance is virologic breakthrough, which is defined as a $>1 \log_{10}$ (10-fold) increase in serum HBV DNA from nadir during treatment in a patient who had an initial virologic response.¹¹ In patients who develop resistance to lamivudine, adefovir should be given immediately once serum ALT level increases. This is especially important in patients with cirrhosis who are at risk of hepatic decompensation. In order to detect the resistance early (before the appearance of detectable serum HBV-DNA by standard assays and before the increase in serum ALT level), monitoring of serum HBV-DNA level by a sensitive assay may be useful. An increase in serum HBV-DNA level of more than 1 log unit generally reflects the appearance of a resistant mutant and allows institution of therapy with adefovir several months before the increase in serum ALT level is observed.¹⁰ The reuse of lamivudine after the emergence of YMDD mutation is still effective in controlling the exacerbation of chronic hepatitis B. The consideration for reusing lamivudine instead of adefovir in our patient was that lamivudine, with a pregnancy risk class B, is less risky than adefovir, which has a class C rating in terms of pregnancy risk.

Currently, 2 types of HBV DNA assays are available as commercial kits: a signal amplification assay in which the signal emitted from captured HBV DNA is amplified, and a target amplification assay which involves amplification of the target HBV DNA sequence.⁵ Quantification of HBV DNA has numerous practical applications, including assessment of disease severity and prognosis, monitoring therapeutic efficacy, and identifying treatment resistance. The development and widespread implementation of sensitive HBV DNA assays have had a significant impact on the ability of physicians to evaluate hepatitis B patients and manage antiviral therapy.⁵

Lamivudine has been found to be an effective treatment strategy for chronic HBV. However, its use is not recommended during the first trimester because animal studies have shown it to be lethal to rabbit fetuses.⁹ Mothers who carry the hepatitis B virus are encouraged to breastfeed their babies. However, it is recommended that breastfeeding start after administration of hepatitis B immune globulin but not necessarily before the first hepatitis B vaccination. Mothers who want to breastfeed should take good care of their nipples to avoid bleeding.

Acknowledgments

This study was supported by research grants from the National Science Council (NSC 94-2314-B-075-014) and Taipei Veterans General Hospital (V96C1-159), Taiwan, R.O.C.

References

1. Balfour HH Jr. Antiviral drugs. *N Engl J Med* 1999;340:1255-68.
2. Liaw YF, Sung JY, Chow WC, Farrell G, Lee CZ, Yuen H, Tanwandee T, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med* 2004;351:1521-31.
3. Liu CJ, Kao JH. Hepatitis B virus-related hepatocellular carcinoma: epidemiology and pathogenic role of viral factors. *J Chin Med Assoc* 2007;70:141-5.
4. Chen HF, Li CY, Chen P, See TT, Lee HY. Seroprevalence of hepatitis B and C in type 2 diabetic patients. *J Chin Med Assoc* 2006;69:146-52.
5. Lan KH. Role of serum quantitative HBV DNA levels in clinical care of CHB patients. *J Chin Med Assoc* 2007;70(Suppl):97-8.
6. Riley LE, Yawetz S. Case 32-2005—a 34-year-old HIV-positive woman who desired to become pregnant. *N Engl J Med* 2005;353:1725-32.
7. Tuomala RE, Shapiro DE, Mofenson LM, Bryson Y, Culnane M, Hughes MD, O'Sullivan MJ, et al. Antiretroviral therapy during pregnancy and the risk of an adverse outcome. *N Engl J Med* 2002;346:1863-70.
8. Watts DH. Management of human immunodeficiency virus infection in pregnancy. *N Engl J Med* 2002;346:1879-91.
9. Su GG, Pan KH, Zhao NF, Fang SH, Yang DH, Zhou Y. Efficacy and safety of lamivudine treatment for chronic hepatitis B in pregnancy. *World J Gastroenterol* 2004;10:910-2.
10. Xu XW, Chen YG. Current therapy with nucleoside/nucleotide analogs for patients with chronic hepatitis B. *Hepatobiliary Pancreat Dis Int* 2006;5:350-9.
11. Chu CJ. Management of chronic hepatitis B-case interactive challenges. *J Chin Med Assoc* 2007;70(Suppl):99-100.