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Telbivudine Prevents Vertical Transmission of Hepatitis B Virus From Women With High Viral Loads: A Prospective Long-Term Study

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BACKGROUND & AIMS: **Hepatitis B virus (HBV) infection is a leading cause of liver diseases. We investigated the efficacy and safety of telbivudine in preventing transmission of HBV from hepatitis B e antigen–positive pregnant women with high viral loads to their infants in an open-label study.**

METHODS: **We performed a prospective study of 450 hepatitis B e antigen–positive pregnant women with HBV DNA levels greater than 10^6 IU/mL; 279 women received telbivudine (600 mg/d) during weeks 24 to 32 of gestation, and 171 women who were unwilling to take antiviral drugs participated as controls. All newborns were vaccinated with a recombinant HBV vaccine and hepatitis B immune globulin, according to a standard immunoprophylaxis procedure. Mother-to-child transmission of HBV was determined by detection of hepatitis B surface antigen and HBV DNA in the infant 6 months after birth.**

RESULTS: **None of the infants whose mothers were given telbivudine tested positive for of hepatitis B surface antigen at 6 months, compared with 14.7% of infants in the control group ($P = 5.317 \times 10^{-8}$). Levels of HBV DNA also decreased among women given telbivudine; 40 of 172 (23.2%) women given telbivudine had undetectable HBV DNA levels before delivery, compared with none of the controls. A significantly higher proportion of women given telbivudine had undetectable levels of HBV DNA in cord blood (99.1%) than controls (61.5%; $P = 1.195 \times 10^{-22}$). No severe adverse events or complications were observed in women or infants.**

CONCLUSIONS: **Telbivudine significantly reduces vertical transmission of HBV from pregnant women to their infants; it is safe and well tolerated by women and infants. Antiretroviral Pregnancy Registry Health Care Providers ID: 26592; Government number: Natural Science Foundation of China (NSFC) 30830090, 30972598; and Third Military Medical University Key Project for Clinical Research: 2012XLC05).**

Keywords: Perinatal; Neonate; Antiviral Drug; Nucleoside Analogue.

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Hepatitis B virus (HBV) infection is one of the most important causes of liver diseases. Nearly 2 billion people worldwide have been infected with HBV, and 350 million have chronic HBV infections, among which 130 million are in China.[1] Perinatal transmission is the primary pathway of HBV infection, particularly in China. The interruption of mother-to-infant transmission (MTCT) is considered to be

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Abbreviations used in this paper: ALT, alanine aminotransferase; anti-HBs, hepatitis B surface antibody; CK, creatine kinase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; MTCT, mother-to-child transmission; NUCs, nucleoside analogues; PCR, polymerase chain reaction.

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important to decrease the individual and population morbidity of HBV infection as well as the global burden of hepatitis B.

Despite the administration of hepatitis B immune globulin and hepatitis B vaccines after birth, 5% to 10% of infants still have a risk of HBV infection.[2] Intrauterine infection cannot be prevented completely by standard passive-active immunoprophylaxis, and it has been shown that there was a positive correlation between high maternal HBV DNA levels and an increased risk of vaccine breakthrough.[3] High maternal viral load is believed to be a key risk factor of MTCT, which has been confirmed in several studies. del Canho et al[4] reported that the effective rate by protective measures could reach 100% if the maternal HBV DNA level was lower than 3.75×10^7 copies/mL (6.70×10^6 IU/mL), however, the protective rate was only 68% if the maternal HBV DNA level was higher than 3.75×10^7 copies/mL, even with passive-active combination immunization. In addition, immunized children born to genotype C HBV–infected mothers may have a higher rate of breakthrough infection than children born to genotype B mothers in Southeast Asia.[5,6]

Recently, antiviral drugs, especially nucleoside analogues (NUCs), have been used in clinical studies to prevent perinatal infection. According to the US Food and Drug Administration, both telbivudine and tenofovir belong to category B, whereas lamivudine, entecavir and adefovir belong to category C, drugs in category B are confirmed safe to fetus, while those in category C are not well defined.[7] Lamivudine first was used in HBV-infected mothers, and showed a satisfactory safety profile in late pregnancy.[8] Telbivudine has potent, specific, and selective anti-HBV activity when administered by an oral route, and no mutagenic, carcinogenic effects, appreciable embryonic, or fetal toxic effects were found, especially in women during their reproductive period.[9,10] Whether the patients were hepatitis B e antigen (HBeAg) positive or negative, telbivudine had a greater antiviral efficacy when compared with lamivudine.[11]

However, few data were available with regard to the efficacy and safety profile of telbivudine in the prevention of MTCT, particularly from long-term prospective studies. The aims of our present study were to evaluate the long-term profile regarding the effectiveness and safety of telbivudine used in HBeAg-positive pregnant women with a high viral load during the second or third trimester of pregnancy.

Patients and Methods

Subjects

We recruited HBV-infected pregnant outpatients from February 2008 to February 2014 at the Department of Infectious Diseases and the Department of Gynecology and Obstetrics in Southwest Hospital (Chongqing, China). The inclusion criteria were as follows: (1) age between 18 and 40 years, mothers were entered into the study between weeks 24 and 32 of gestation; (2) testing positive for serum hepatitis B surface antigen (HBsAg) and HBeAg; and (3) HBV DNA levels of 10^6 IU/mL or greater. The exclusion criteria were as follows: co-infection with hepatitis C virus, hepatitis D virus, hepatitis A virus, hepatitis E virus, human immunodeficiency virus, or co-existed with other liver diseases (drug induced hepatitis, non-alcoholic steatohepatitis, auto immune hepatitis, ntrahepatic cholestasis of pregnancy et al); and evidence of fetal dysplasia. All the subjects in the telbivudine group were registered in the Antiretroviral Pregnancy Registry (HCP ID: 26592).

A total of 279 HBeAg-positive mothers received telbivudine (Novartis, Inc, Basel, Switzerland) 600 mg; mothers were entered into the study between weeks 24 and 32 of gestation and then continued to receive treatment with telbivudine until delivery or up to a month thereafter. Meanwhile, 171 pregnant women who were unwilling to take antiviral drugs served as the controls. All infants were vaccinated with recombinant HBV vaccines (10 μg) after birth, at weeks 4 and 24. In addition, they received hepatitis B immune globulin (200 IU) at birth and at 1 month.

Laboratory Tests

Maternal serum HBV markers (HBsAg, hepatitis B surface antibody [anti-HBs], HBeAg, hepatitis B e antibody, and hepatitis B c antibody), HBV DNA levels, alanine aminotransferase (ALT), aspartate aminotransferase, and creatine kinase (CK) were detected at the beginning of telbivudine treatment, then once a month until 1 month after delivery. These markers also were measured in the untreated controls. Details of the obstetric examination were recorded at each antepartum visit.

Neonatal HBV markers and HBV DNA levels were tested in umbilical cord blood at birth; and HBV markers, liver biochemical tests, and hematologic tests also were measured at 3, 6, and 12 months, and thereafter. If HBV markers, except for anti-HBs, were positive, then HBV DNA was detected afterward. The infant's development including respiratory rate, weight, length, breast feeding status, intelligence quotient, and so forth were evaluated at each visit during the follow-up period. Adverse events also were timely recorded.

Serum HBV DNA levels were detected using real-time quantitative fluorescence probing polymerase chain reaction (PCR) (Lightcycler; Roche Diagnostics Co, Ltd, Sandhofer, Switzerland), with a detection range from 1×10^2 to 1×10^8 IU/mL. Considering the limitation of real-time quantitative fluorescence PCR in low viral load is less than 1×10^2 IU/mL, we used the COBAS Amplicor HBV Monitor PCR (Roche Diagnostics Co, Ltd), with a threshold of less than 0.5×10^2 IU/mL for these samples. HBV markers were detected by Elecsys 2010 analyzer (Roche Diagnostics Co, Ltd). Liver