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Growth and development of children prenatally exposed to telbivudine administered for the treatment of chronic hepatitis B in their mothers

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SUMMARY

Objectives: We studied the growth and development of children prenatally exposed to telbivudine used to treat chronic hepatitis B virus (HBV) infection in their mothers.
Methods: Maternal abnormalities during pregnancy and delivery and infant congenital anomalies, physical development status, developmental quotient (DQ), HBV vertical transmission status, and HBV vaccination outcomes of 54 infants were evaluated (2010–2013).
Results: No fetal abnormalities were observed during pregnancy or delivery. Postpartum, three infants (5.56%) had abnormalities: ankyloglossia, cutaneous hemangioma, and vaginal canal leak. Height and weight were within the normal range at birth and at 6 weeks, but were higher than the reference at 12 months ($p < 0.05$). Body mass index increased gradually with age ($p < 0.05$). DQ scores were normal (84.81%, 229/270) in 37 children (68.52%), abnormal or suspicious for a developmental delay (15.19%, 41/270) in 17 children (31.48%), and indicated a developmental delay (4.07%, 11/270) in seven children (12.96%). There were no significant differences in developmental delay between children prenatally exposed to telbivudine and controls ($p > 0.05$). HBV vertical transmission was successfully blocked in all infants. The effective HBV vaccination rate was 98.15% (53/54).
Conclusions: The growth and development of children prenatally exposed to telbivudine was normal, indicating that telbivudine treatment during pregnancy is safe and effective.

1. Introduction

Chronic hepatitis B virus (HBV) infection is an infectious disease that affects approximately two billion people worldwide; in addition, 350 million people are chronic carriers of the virus.[1] Furthermore, the prevalence of hepatitis B surface antigen (HBsAg) positivity among fertile women in some highly epidemic areas, such as Africa and Asia, can be as high as 9.2–15.5%, and in China the prevalence is 11.0%. Chronic HBV-infected fertile women may require antiviral treatment during pregnancy.[1–4]

Telbivudine (L-deoxythymidine; LdT) is an approved oral nucleoside analog (NA) used to inhibit HBV within the cytoplasm that has been assigned to pregnancy category B by the US Food and Drug Administration; therefore, it can be used during pregnancy. For some chronic HBV-infected women who become pregnant during the NA treatment period and for whom conservative treatment is not recommended, discontinuing the antiviral treatment during pregnancy would result in possible exacerbation of hepatic disease and threaten the safety of both the mother and infant.[4–6] Therefore, NA treatment in these women should be used during pregnancy, either in late pregnancy only or throughout the entire pregnancy. The risk of HBV perinatal transmission is highest in women with high levels of viremia,[7,8] and some pregnant women with a high HBV viral load take an NA to lower the risk of HBV vertical transmission, usually commencing in the third trimester.[9,10] All of the fetuses in these pregnancies experience intrauterine exposure to the NA, which may affect fetal development.

Lamivudine and LdT, as NAs, significantly reduce viral loads and vertical transmission and have favorable safety profiles in

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pregnancy.[11–16] However, there are very few reports regarding the growth and development of children prenatally exposed to LdT. The present study aimed to evaluate the growth and development of children exposed to LdT in the fetal period to provide insights into the efficacy and safety of LdT use in the perinatal period.

2. Materials and methods

2.1. Patients

From January 1, 2010 to May 1, 2013, 54 children delivered to mothers with chronic HBV infection who received LdT treatment during their pregnancy at Beijing Ditan Hospital were enrolled in this study. Three mothers had experienced abnormalities during a previous pregnancy: hydatidiform mole in two mothers and sebaceous adenoma resection in one mother. Twenty mothers continued existing LdT treatment throughout their pregnancy because they could not stop treatment while pregnant. Nine mothers had received another NA or interferon treatment but later had virological breakthrough and liver function rebound and switched to LdT treatment in pregnancy. Twenty-five mothers had never taken any NA treatment, but used LdT in late pregnancy at a gestational age >28 weeks because of the results of laboratory tests (alanine aminotransferase <2 times the normal upper limit of the reference range and HBV DNA $>1 \times 10^5$ copies/ml). All mothers were chronic hepatitis B patients without compensated cirrhosis. None of the mothers were co-infected with hepatitis C virus, hepatitis delta virus, HIV, syphilis, toxoplasmosis, rubella, cytomegalovirus, Epstein–Barr virus, or herpes simplex virus, and none had an endocrine or metabolic disease, organ failure, or were drug abusers. All of the mothers underwent routine pregnancy examinations and took nutritional supplements during pregnancy, including folic acid during early pregnancy to prevent embryonic neural tube defects. Demographic characteristics and basic clinical information, including HBV infection status and treatment history, are summarized in Table 1. The mothers and their infants were divided into two groups: those taking LdT during their entire pregnancy (early-pregnancy treatment group) and those taking LdT only during late pregnancy (late-pregnancy treatment group).

An additional 54 children delivered to mothers with chronic HBV infection who did not receive LdT treatment during their pregnancy were selected as controls. The children's parents were matched by age and educational level. In addition, a congenital anomalies observation control group included infants born to mothers with chronic HBV infection who did not receive NA treatment during their pregnancy at Beijing Ditan Hospital between January 1, 2010 and December 31, 2010 ($n = 2747$) and between January 1, 2011 and December 31, 2011 ($n = 2567$).

Table 1
Clinical information of mothers treated with telbivudine during pregnancy

	Observed population ($N = 54$)
Average age, years	30.45 ± 3.82
Primipara, *n* (%)	25 (46.29)
Cirrhosis, *n* (%)	0 (0)
HBeAg positivity rate, *n* (%)	40 (74.07)
HBV DNA $>10^5$ copies/ml in early pregnancy, *n* (%)	25 (46.30)
HBV DNA $>10^5$ copies/ml before delivery, *n* (%)	4 (7.41)
Treatment before pregnancy, *n* (%)	
Naive	25 (46.29)
ADV	5 (9.26)
LAM→ADV	4 (7.41)
IFN + LdT	1 (3.70)
LdT	20 (37.03)

ADV, adefovir dipivoxil; HBeAg, HBV e antigen; HBV, hepatitis B virus; IFN, interferon; LAM, lamivudine; LdT, telbivudine.

2.2. Methods

All mothers underwent routine screening tests, including assessments of liver function and HBV serology (HBV markers and HBV DNA) every 12 weeks. All adverse events that occurred during pregnancy and delivery were recorded.

Our evaluation of the growth and development of all infants started at delivery and continued for at least 12 months. Assessments included the occurrence of adverse events in the infants during different periods, congenital and developmental anomalies, physical development status (weight and height), developmental quotient (DQ), HBV vertical transmission status, and HBV vaccination outcomes.

The infants' clinical data, including average gestational age, delivery mode, Apgar score, physical development status, and adverse events during the neonatal period and infancy, were recorded. The physical development status of the infants was evaluated at three time points: immediately after birth and at 6 weeks and 12 months of age.

Congenital and developmental anomalies were identified by physical examination, hearing screening, and laboratory tests, in addition to renal screening, if necessary, for at least 24 months.

The neurodevelopment of infants was evaluated by the DQ using the Gesell Developmental Schedules (GDSs), which include reflexes and reactions (voluntary, spontaneous, or learned), as well as postural reactions, locomotion, and coordination, constructive ability (which is influenced by motor development), and visible and audible communication; individual reactions regarding people and stimulations (depending mainly on the temperament of the child and the surroundings) were also evaluated. The results are expressed as scores for the five domains assessed: adaptability, gross motor skills, fine motor skills, language, and sociability. Each child was assigned a DQ in each of the five areas, resulting in a total of 270 items for the 54 children. A score <85 indicates a suspicion of developmental delay, and a score <75 indicates a developmental delay.[4] Testing was conducted by trained DQ test professionals to maximize reliable assessment and valid interpretation, minimizing both inter- and intra-examiner variability.

Liver function, HBV serology, and HBV DNA of infants were measured twice: at birth and 1 month after the HBV vaccinations were completed (7–8 months). The rate of blocking vertical transmission of HBV and the outcomes of HBV vaccination were confirmed and analyzed.

2.3. Laboratory tests

Liver function and HBV serology were tested in the hospital's clinical laboratory. HBV DNA was detected with a real-time PCR amplification kit (Kehua Biological Company, Shanghai, China), which can detect HBV DNA levels as low as 500 copies/ml. HBV markers were detected using ELISA kits (Abbot Laboratories, North Chicago, IL, USA) on an ARCHITECT i2000 automatic immunoassay analyzer (Abbott), in accordance with the manufacturer's instructions.

Hearing screenings were performed with the Echo-Screen (Madsen Company, Germering, Germany).

Peripheral blood samples were spotted onto filter paper, and the specimens were sent to the Beijing Neonatal Diseases Screening Center to rule out congenital phenylketonuria and hypothyroidism by liquid chromatography tandem mass spectrometry detection. Five types of congenital disease (hearing defects, congenital heart disease, congenital hip dislocation, congenital hypothyroidism, and phenylketonuria) were assessed.