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 (68.52%), 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.

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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 endemic 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. 5–7 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, 8,9 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. 10,11 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...
pregnancy.12–18 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 × 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, cyto-
megalovirus, 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).

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, con-
structive ability (which is influenced by motor development), and
visible and audible communication; individual reactions regarding
people and stimuli (depending mainly on the tempera-
ment 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.5 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
tested 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 instruc-
tions.

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.
2.4. Statistical analysis

The statistical analysis was performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Measurement data are expressed as the mean and standard deviation and were compared with analysis of variance or t-tests. Fisher’s exact test was used for the comparison of rates. A p-value of <0.05 was considered statistically significant.

3. Results

3.1. Maternal baseline characteristics and adverse events during pregnancy

The average LdT treatment times in the early-pregnancy treatment and late-pregnancy treatment groups were 38.05 ± 1.54 weeks (range 36-41 weeks) and 10.43 ± 1.02 weeks (range 9–11 weeks), respectively.

No development retardation was found in any fetus with ultrasound monitoring during pregnancy. One mother underwent in vitro fertilization with the transfer technique and delivered a female infant. Another mother had a threatened abortion, but symptoms of miscarriage disappeared after aggressive treatment.

The most common adverse events for mothers during pregnancy were gestational diabetes (16/54, 29.62%), viral hepatitis (7/54, 12.96%), pregnancy cholestasis syndrome (6/54, 11.1%), and premature rupture of the membranes (4/54, 7.41%). Other adverse events included hyperemesis gravidarum, moderate-to-severe anemia (hemoglobin level <9 g/l), edema, polyhydramnios, vulvar abscess, and common cold.

In the late-pregnancy treatment group, 20 of 25 mothers had HBV DNA >1 × 10^5 copies/ml. The viral load of all of the cases decreased after LdT treatment, and 11 cases had no detectable HBV viremia at antepartum testing (HBV DNA <500 copies/ml). In the early-pregnancy treatment group, 17 of 29 cases had HBV DNA >5 × 10^5 copies/ml in early pregnancy, and the viral load decreased after LdT treatment; at antepartum testing, 27 cases had no HBV viremia and two had a viral load of 5.75 × 10^5 copies/ml.

3.2. Clinical characteristics and adverse events during the neonatal period

The average gestational age of the infants was 39 ± 1.41 weeks, with one neonate delivered preterm at 36 weeks without complications. Sixteen of the 54 infants were born by cesarean delivery. Normal Apgar scores at delivery were recorded, with only one neonate with blue asphyxia and an Apgar score of 7; the blue asphyxia symptoms disappeared after aggressive treatment, and the subsequent 5- and 10-min Apgar scores were normal.

The most common adverse events for infants were nuchal cord (13/54, 24.07%) and premature rupture of the membranes (4/54, 7.41%). Other adverse events included extremely long umbilical cord and caput succedaneum. There were no fetal developmental abnormalities reported around the time of delivery.

3.3. Congenital dysplasia and adverse event monitoring

All 54 infants were followed up for more than 12 months, 11 were followed up for more than 2 years, and one was followed up for more than 3 years. None of the infants had abnormal hearing, congenital phenylketonuria, hypothyroidism, congenital heart disease, or congenital hip dislocation. Three infants in the early-pregnancy treatment group had abnormalities postpartum: one infant with ankyloglossia without delayed language development whose parents planned to arrange surgery when he was 2 years old and one infant with a 3 × 3-cm cutaneous hemangioma on the right foot after 4–5 months of topical therapy that disappeared when the infant was 7 months old. Another infant was born with vaginal canal leak underwent successful surgery when the infant was 1 month old. Other infants showed no signs of abnormal congenital dysplasia. Thus, the abnormality rate of all infants in this study was 5.56% (3/54). There were no significant differences in the abnormality rates between the children observed in this study and the controls in 2010 (72/2747, Chi-square = 1.569, p > 0.403) or 2011 (50/2567, Chi-square = 3.46, p = 0.090).

The most common adverse events for infants younger than 6 weeks old were eczema (14/54, 25.92%) and hypocalcemia (11/54, 20.37%). The most common adverse events for infants younger than 12 months old were respiratory tract infections (7/30, 23.33%), diabetes (5/54, 9.25%), and eczema (4/54, 7.41%). Other adverse events in infants included nasal obstruction, neonatal pneumonia, myocardial damage, newborn infection, and inguinal hernia. One case in the late-pregnancy treatment group had language retardation; this patient had delayed language abilities without a nervous disorder.

3.4. Physical development status during infancy

Height and weight increased gradually with age during the first 12 months (Table 2). The physical development status of 98.15% of the neonates was in the normal range; two infants had macrosomia without complications such as hypoglycemia. There were no small-for-gestational-age neonates. The height of only one female neonate was 53 cm higher than the reference range. There were no significant differences between the average weights and heights of neonates and the reference values of the World Health Organization (WHO) 2006 child growth standards (p > 0.05). There were no significant differences between the early-pregnancy treatment and late-pregnancy treatment groups in physical development status or adverse events during the neonatal period (p > 0.05).

No growth retardation cases were observed during the infancy period. The average height and weight of the infants were in the normal range at delivery and at 6 weeks of age, but were higher at 12 months.

| Table 2: Height and weight of children prenatally exposed to telbivudine administered to treat chronic hepatitis B in their mothers |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                  | At birth        | At 6 weeks      | At 12 months    |                  |
| Height, cm (N=54) | Average         | Highest         | Lowest          | Average          |
|                  | 50.42 ± 1.03    | 57.75 ± 2.37    | 77.98 ± 2.25    | 3.31 ± 0.82      |
|                  | 53              | 63              | 81.7            | 4.25            |
|                  | 47              | 53              | 70              | 2.65            |
| Average, boys    | 50.67 ± 1.12    | 57.63 ± 2.72    | 78.5 ± 1.52     | 3.58 ± 0.30      |
| Average, girls   | 49.99 ± 1.11    | 57.82 ± 2.01    | 77.93 ± 2.14    | 3.06 ± 0.65      |
| Normal cases (%) | 53 (98.15)      | 50 (92.59)      | 53 (98.15)      | 54 (100)         |
| Weight, kg (N=54) | Average         | At 6 weeks      | At 12 months    |                  |
|                  | 3.31 ± 0.82     | 5.15 ± 0.58     | 10.2 ± 0.91     |                  |
|                  | 4.25            | 6.4             | 11.6            |                  |
|                  | 2.65            | 3.95            | 7.5             |                  |
| Average, boys    | 3.58 ± 0.30     | 5.29 ± 0.35     | 10.50 ± 1.02    |                  |
| Average, girls   | 3.06 ± 0.65     | 5.00 ± 0.60     | 10.24 ± 0.40    |                  |
| Normal cases (%) | 54 (100)        | 53 (98.15)      | 54 (100)        |                  |

Table 3
Body mass index of children prenatally exposed to telbivudine administered for the treatment of chronic hepatitis B in their mothers

<table>
<thead>
<tr>
<th>Age</th>
<th>BMI (N=54)</th>
<th>Normal cases (%)</th>
<th>Average</th>
<th>Highest</th>
<th>Lowest</th>
<th>Early-pregnancy treatment group (n=29)*</th>
<th>Late-pregnancy treatment group (n=25)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>At birth</td>
<td>54 (100%)</td>
<td>13.49 ± 1.04a</td>
<td>15.1</td>
<td>11.2</td>
<td>13.41 ± 1.61</td>
<td>13.62 ± 2.21</td>
<td></td>
</tr>
<tr>
<td>6 weeks</td>
<td>53 (98.15)</td>
<td>15.22 ± 1.49a</td>
<td>18.85</td>
<td>11.05</td>
<td>15.84 ± 1.65</td>
<td>14.19 ± 3.12</td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>53 (98.15)</td>
<td>16.69 ± 1.54a</td>
<td>21.22</td>
<td>14.63</td>
<td>16.55 ± 1.36</td>
<td>16.82 ± 1.22</td>
<td></td>
</tr>
</tbody>
</table>

BMI, body mass index.

* Early-pregnancy treatment group: children whose mothers took telbivudine during their entire pregnancy.

** Late-pregnancy treatment group: children whose mothers took telbivudine only during late pregnancy.

than the reference range at 12 months of age (p < 0.05). The physical development status of 92.59% of the infants was in the normal range at 6 weeks of age. Of two infants with heights 63 cm higher than the reference value, one was 6.4 kg heavier than the reference. The other two infants had heights 54.5 and 53 cm lower than the reference value at 6 weeks of age. The physical development status of 98.15% of the infants was in the normal range at 12 months of age; only one infant had a height 81.7 cm higher than the reference.

The body mass index (BMI) of both groups increased gradually with age (p < 0.05) (Table 3). BMI was in the normal range for the majority of the children; only one male infant at 6 weeks had a BMI 11.05 kg/m² lower than the 95% reference range, and one infant at 12 months had a BMI 21.22 kg/m² higher than the 95% reference range. There were no significant differences in BMI between the early-pregnancy treatment and late-pregnancy treatment groups during infancy (p > 0.05).

3.5. DQ monitoring

The normal DQ was 100 ± 15 (Figure 1); 84.81% (229/270) of the DQ scores in 68.52% (37/54) of the children were normal. In 17 (31.48%) children, 15.19% (41/270) of the DQ scores indicated either a developmental delay or a suspicion of a developmental delay. Eleven infants (4.07%, 11/270) were <75, indicating a developmental delay.

**Figure 1.** Development quotient (DQ) scores of children prenatally exposed to telbivudine administered for the treatment of chronic hepatitis B in their mothers. Each patient was assessed for the five DQ scores, including adaptability, gross motor skills, fine motor skills, language, and sociability, totaling 270 items for 54 patients. A score <75 indicates a developmental delay and a score ≥75 and <85 indicates a suspicion of a developmental delay. Eleven items (4.07%, 11/270) for seven children (12.96%, 7/54) prenatally exposed to telbivudine were <75, indicating a developmental delay.

Table 4
Development quotient (DQ) of children prenatally exposed to telbivudine administered for the treatment of chronic hepatitis B in their mothers

<table>
<thead>
<tr>
<th>DQ (N=54)</th>
<th>Highest</th>
<th>Lowest</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adaptability</td>
<td>117</td>
<td>75</td>
<td>94.64 ± 10.30</td>
</tr>
<tr>
<td>Gross motor skills</td>
<td>132</td>
<td>70</td>
<td>99.09 ± 13.94</td>
</tr>
<tr>
<td>Fine motor skills</td>
<td>124</td>
<td>69</td>
<td>99.35 ± 11.25</td>
</tr>
<tr>
<td>Language competence</td>
<td>127</td>
<td>58</td>
<td>95.17 ± 12.65</td>
</tr>
<tr>
<td>Social skills</td>
<td>126</td>
<td>73</td>
<td>100.44 ± 14.79</td>
</tr>
<tr>
<td>Total (N=54)</td>
<td></td>
<td></td>
<td>95.97 ± 10.78</td>
</tr>
<tr>
<td>Early-pregnancy treatment group (n=29)*</td>
<td></td>
<td></td>
<td>93.12 ± 9.74</td>
</tr>
<tr>
<td>Late-pregnancy treatment group (n=25)b</td>
<td></td>
<td></td>
<td>97.84 ± 13.76</td>
</tr>
</tbody>
</table>

* Early-pregnancy treatment group: children whose mothers took telbivudine during their entire pregnancy.

b Late-pregnancy treatment group: children whose mothers took telbivudine only during late pregnancy.

Table 5
Development quotient (DQ) of children prenatally exposed to telbivudine, compared with controls

<table>
<thead>
<tr>
<th>Developmental delay</th>
<th>Number</th>
<th>Patients</th>
<th>Controls</th>
<th>c2</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DQ &lt;75, %</td>
<td>Cases (N=54)</td>
<td>7 (12.96)</td>
<td>2 (1.70)</td>
<td>3.03</td>
<td>0.16</td>
</tr>
<tr>
<td>Suspicion of developmental delay</td>
<td>DQ test items (n=270)</td>
<td>11 (4.07)</td>
<td>4 (1.48)</td>
<td>3.36</td>
<td>0.11</td>
</tr>
<tr>
<td>75 ≤ DQ &lt; 85, %</td>
<td>Cases (N=54)</td>
<td>10 (18.52)</td>
<td>3 (5.55)</td>
<td>4.29</td>
<td>0.07</td>
</tr>
<tr>
<td>Abnormality in all</td>
<td>DQ test items (n=270)</td>
<td>30 (11.11)</td>
<td>9 (3.31)</td>
<td>12.19</td>
<td>0.00</td>
</tr>
<tr>
<td>DQ &lt; 85, %</td>
<td>Cases (N=54)</td>
<td>17 (31.48)</td>
<td>5 (9.26)</td>
<td>8.22</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>DQ test items (n=270)</td>
<td>41 (15.19)</td>
<td>13 (4.81)</td>
<td>16.13</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Q14

3.6. Prevention of mother-to-infant transmission and HBV vaccinations

Liver function, HBV serology, and HBV DNA of the children were evaluated at 7–8 months of age. No HBsAg-positive cases were found, and vertical transmission was successfully blocked in 54 infants, for a blocking rate of 100%. A quantitative HBV surface antibody (anti-HBs) test revealed effective vaccination (anti-HBs-positive) in 53 infants in our study, with maximum and minimum titers of 1000 and 127.21 mIU/l, respectively. The effective vaccination rate of the infants in our study was 98.15% (53/54), with no differences between the early-pregnancy treatment and late-pregnancy treatment groups (p > 0.05). Only one infant whose parents were both chronic HBV-infected and whose mother had taken LdT throughout her pregnancy was anti-HBs-negative, and the vaccination failed. After enhanced HBV vaccination at age 8 months, the infant’s anti-HBs titer increased to 127.8 mIU/ml at 12 months of age.

4. Discussion

Although there have been a number of studies regarding the safety of LdT treatment in pregnancy,12–18,20 very few have been reported regarding the growth and development of children delivered to chronic HBV-infected women treated with LdT. The abnormality rate in all of the infants in the present study was similar to that of infants born to mothers without or with HBV infection (5.1–6.3% and 7.2–10%, respectively) in previous reports.21–23 LdT treatment is reportedly effective for blocking HBV mother-to-infant transmission (MTIT). For infants born to hepatitis B e antigen (HBeAg)-positive mothers, vertical transmission was not blocked in 7–16.3% of women with a high HBV viral load during pregnancy faced with a high risk of MTIT, even after receiving passive–active immunoprophylaxis with hepatitis B immunoglobulin and three doses of hepatitis B vaccine.24 In a previous study, none of the infants whose mothers received LdT had immunoprophylaxis failure, whereas 8.6% of the infants of control mothers did (p = 0.029) in an open-label, prospective study of 88 HBeAg-positive pregnant women with chronic HBV infection, HBV DNA levels >6 log10 copies/ml, and increased levels of alanine aminotransferase.14 Another study of LdT treatment throughout pregnancy reported that none of 39 of 52 live infants followed up for more than 6 months and who completed all examinations for MTIT were found to have HBSAg positivity, indicating a 100% blocking rate.15 In the present study, the HBV viral load of the pregnant women who received LdT treatment decreased, whether during their entire pregnancy or late pregnancy, and the HBSAg and HBV DNA of all 54 infants were negative, resulting in a 100% HBV MTIT blocking rate. Furthermore, the HBV vaccination was successful in infants exposed to LdT in utero, with 98.15% of the infants protected against hepatitis B and no differences in anti-HBs titer between the infants exposed to LdT throughout the entire pregnancy and those exposed only in late pregnancy.30

Drug abuse is a primary contributor to birth defects in China.25 The congenital abnormality rates for infants born to mothers without or with HBV infection are 5.1–6.3% and 7.2–10%, respectively.21–23 An overall rate of congenital abnormalities of 3.8% (2/53) has been reported in infants whose mothers took LdT for chronic HBV throughout pregnancy.15 In our study, none of the infants had abnormal hearing, congenital phenylketonuria, or hypothyroidism in follow-up periods lasting...
more than 12 months and some up to 48 months. Congenital dysplasia was detected in three cases within the neonatal period, resulting in a congenital abnormality rate of 5.5%, which is similar to that of women without or with HBV infection in previous reports. In addition, there were no significant differences in congenital dysplasia between children exposed to LdT and the controls. Hemangioma, abnormal lingual frenulum, and vaginal canal leak were found in three of our infants, all in the early-pregnancy treatment group. One patient in the late-pregnancy treatment group had delayed language abilities without a nervous disorder. No other genetic metabolic diseases or congenital defects were found. Therefore, our observations do not support a relationship between LdT exposure and birth defects or genetic disease; however, additional large-sample studies are warranted, especially in children exposed to LdT throughout pregnancy.

The physical development status of the majority of the neonates was in the normal range at delivery and 6 weeks of age, as measured by weight and height. Moreover, no cases with growth retardation were observed during the infancy period. The average weight and height of the infants were higher than WHO standard values (2006) at 12 months of age, similar to the findings presented in a previous report on infants in Beijing. Furthermore, the BMI of the infants in our study increased gradually with age. These observations suggest that LdT treatment in pregnancy does not affect the physical development of infants.

Follow-up neurodevelopmental assessments in neonates exposed to adverse factors, particularly drugs, are very important because prenatal exposure can result in abnormal neurological developmental processes in infants. For example, neonatal neurobehavioral development is affected by intrauterine low-level lead exposure, and prenatal exposure to elevated levels of pyrethroid pesticides is associated with reduced neurodevelopment in infants. In addition, anti-thyroid treatment during pregnancy may have adverse effects on the infant’s DQ. In the present study, 84.81% of the overall DQ scores were normal; however, in 17 children, the DQ scores suggested either developmental delay (n = 7) or were suspicious for a developmental delay (n = 10). Abnormally low scores were spread throughout the GDS regions, with no dominant abnormal regions. Moreover, there were no differences between the cases and controls, and the rate of abnormal scores was similar to that of 13.1% in 2330 infants in a previous report. Therefore, the DQs of children delivered to chronic HBV-infected women treated with LdT were normal, suggesting that LdT did not affect the neurodevelopment of these infants.

However, the combined developmental delay and suspicious for a developmental delay rates in the present study were higher in the children prenatally exposed to LdT than the controls. Because development activity exists along a continuous spectrum in every child, the final developmental assessment results may be normal for most infants with mildly or moderately delayed development, especially for those with a marginal status. However, intervention and follow-up are necessary when infants exposed to LdT during pregnancy have a lower DQ. Future, larger samples of infants exposed to LdT throughout pregnancy are necessary to discern any differences in DQ.

The findings of the present study indicate that the growth and development of children of chronic HBV-infected mothers who are prenatally exposed to LdT are normal, indicating that LdT treatment increases the HBV MTIT blocking rate but does not increase the incidence of congenital abnormalities or affect the physical and neurological development of the infants. LdT treatment during pregnancy in mothers with chronic hepatitis B is safe and effective for infants. However, larger sample sizes are needed in future observations to provide greater insight into the
growth and development of children prenatally exposed to NAs, including LdT.

Conflict of interest: All authors declare no financial or personal relationships with other people or organizations that could inappropriately influence (bias) their work.

References


