

# Telbivudine treatment of hepatitis B virus-infected pregnant women at different gestational stages for the prevention of mother-to-child transmission

## Outcomes of telbivudine treatment during pregnancy

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### Abstract

This prospective study evaluated the viability of telbivudine for blocking mother-to-child transmission (MTCT) of hepatitis B virus (HBV) infection.

Pregnant women positive for the hepatitis B surface antigen began telbivudine treatment before 14 weeks of gestation (i.e., early), between 14 and 28 weeks of gestation (late), or not at all (control). In the late-treatment group, 55 women terminated telbivudine therapy within puerperium. All neonates underwent routine hepatitis B immunoglobulin plus vaccination. Mothers and infants were followed for 7 months after birth.

Pregnancy outcomes were similar among the 3 groups. HBV MTCT rates in the early and late treatment and control groups were 0, 0, and 4.69%, respectively. The rates of infant vaccination success among the 3 groups were similar, as were neonatal outcomes including birth weights, asphyxia, hyperbilirubinemia, Apgar score, birth defects, and weight and height at 7 months. Puerperal discontinuation of telbivudine did not increase the alanine transaminase value at 7 months after birth, but increased serum HBV DNA levels, and rates of positive hepatitis Be-antigen.

Telbivudine treatment in HBV-infected pregnant women was associated with lower serum HBV DNA levels and reduced rates of HBV MTCT; there were no associated changes in pregnancy or neonatal outcomes at birth or 7 months after birth, or in the rate of infant vaccination success. Puerperal drug withdrawal after short-term antiviral therapy will not influence hepatic function, but may increase virus replication.

**Abbreviations:** ALT = alanine transaminase, BUN = blood urea nitrogen, CK = creatine kinase, Cre = creatinine, ELISA = enzyme-linked immunosorbent assay, HBeAg = hepatitis Be-antigen, HBIG = hepatitis B immunoglobulin, HBIG plus HBV vaccination = combined immunization, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HBV serological markers = HBsAg, anti-HBs, HBeAg, anti-HBe, and anti-HBc, MTCT = mother-to-child transmission.

**Keywords:** antiviral therapy, hepatitis B virus, mother-to-child transmission, pregnancy

## 1. Introduction

Approximately 360 million people worldwide are chronically infected with hepatitis B virus (HBV), resulting in substantial

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morbidity and ~600,000 deaths per year.<sup>[1,2]</sup> The prevalence of HBV infection is particularly high in Africa and Asia. In endemic areas, mother-to-child transmission (MTCT) is the major source of new infection. Even in countries with low endemic rates such as Europe and the United States, over one-third of infections can still be attributed to MTCT.<sup>[1]</sup> In China, approximately 11.2% to 12.5% of pregnant women test positive for the hepatitis B surface antigen (HBsAg). Among these, the positive rate for hepatitis Be-antigen (HBeAg) is about 20% to 30%.<sup>[3]</sup>

The standard strategy for preventing HBV perinatal transmission in HBsAg-positive mothers is passive vaccination with hepatitis B immunoglobulin and active immunization by HBV vaccine. Although this active-passive immunoprophylaxis is very effective, it still does not completely prevent the vertical transmission of HBV. It is reported that in highly viremic mothers, failure of passive-active immunoprophylaxis of infants can occur, even with full compliance, and the failure rate is 10% to 15%.<sup>[4]</sup>

Intrauterine infection is an important cause of vaccine failure in vertical transmission.<sup>[5,6]</sup> HBV DNA is a direct marker of viral replication and host infectivity, and numerous studies have found that high HBV DNA levels, generally in pregnant women positive for HBeAg, are a risk factor for MTCT.<sup>[7-9]</sup> Rates of vertical transmission are high in pregnant women with high HBV DNA levels.<sup>[10]</sup> Thus, it is recommended that antiviral therapy can be used for mothers with high HBV DNA levels.<sup>[11,12]</sup> Antiviral therapy in pregnant women with high HBV DNA levels can

rapidly inhibit HBV replication and decrease the serum HBV DNA load, decreasing rates of MTCT.

For the prevention of perinatal and intrauterine HBV transmission in highly viremic HBsAg-positive women, antiviral therapy is generally administered in the second or third trimester of pregnancy. In this way, the serum HBV DNA levels of these mothers are effectively reduced.<sup>[13,14]</sup>

Nucleoside analogs with similar structure, but no nucleoside function, can competitively inhibit the synthesis and extension of DNA, resulting in lower HBV DNA levels. The nucleoside analog telbivudine is a reverse transcriptase inhibitor with no effect on human nucleotide or DNA synthesis.<sup>[15]</sup> Studies also have shown that telbivudine has no carcinogenic, teratogenic, or mutagenic effects and does not adversely affect fetal development.<sup>[16]</sup> However, there is little relevant data available from human pregnancy registries regarding the use of telbivudine. Current guidelines for the management of HBV-infected pregnant women recommend initiating antiviral therapy with a nucleoside analogue during the last trimester.<sup>[17]</sup>

There are controversial aspects regarding antiviral therapy for HBV during pregnancy. For example, several studies have shown that MTCT still occurs in HBV-infected women, although the anti-HBV therapy was administered during pregnancy.<sup>[18–20]</sup> Yet, the number of studies that have focused on anti-HBV therapy during early pregnancy is very limited; therapy usually begins in middle or late pregnancy, which may be too late to prevent intrauterine HBV infection that occurs earlier.

Also, most investigations only monitored hepatic function and HBV DNA levels in mothers, and there is insufficient long-term follow-up data for infants of mothers treated during the pregnancy. Another issue is that during the course of long-term anti-HBV, there is a risk of mutation of the virus that could lead to drug resistance. In addition, long use of antiviral medication may affect breast-feeding in HBV-infected women, and add to the economic burden.

The answers to several essential questions remain elusive: Is antiviral therapy necessary for HBV-infected pregnant women?; When should antiviral therapy start and end?; and, When antiviral therapy is administered during pregnancy, what are the long-term outcomes in mothers and infants? In the present prospective study, HBV-infected women were treated with the nucleoside analogue telbivudine, starting from early or middle pregnancy, and this antiviral therapy in some of the women was terminated within puerperium. To determine whether telbivudine therapy during pregnancy is appropriate for HBV-infected women, we evaluated its effects on MTCT and the outcomes of mothers and infants, and the effects of its withdrawal in mothers during puerperium.

## 2. Materials and methods

This prospective study was approved by the institutional review board at Third Affiliated Hospital, Sun Yat-sen University. All mothers enrolled in this study provided written informed consent, and parents gave consent for their children to participate in this study.

### 2.1. Inclusion and exclusion criteria

HBsAg-positive pregnant women were recruited from January 2012 to March 2015 in the Department of Obstetrics and Gynecology, Third Affiliated Hospital, SunYat-sen University. The following were the criteria for inclusion: pregnant women

aged  $\geq 20$  years, and serum-positive for HBsAg. Potential participants were excluded for use of immunomodulator or cytotoxic drugs; long-term use of glucocorticoid drugs during pregnancy; newborns without combined immunization (hepatitis B immunoglobulin plus HBV vaccination) within 24 hours of birth; a HBsAg-positive father; or a mother coinfecting with hepatitis C virus, hepatitis D virus, or human immunodeficiency virus.

### 2.2. Early-treatment group

The subjects who were treated with the nucleoside analogue telbivudine starting before 14 weeks of gestation, and their infants, constituted the early-treatment group ( $n = 34$ ). This group included 8 women who were treated with telbivudine before 14 weeks of gestation due to active hepatitis; 17 who received telbivudine treatment before pregnancy and remained on this treatment after a confirmation of pregnancy; and 5, 3, and 1 woman who received lamivudine, entecavir, and adefovir treatment, respectively, before pregnancy and changed to telbivudine after a confirmation of pregnancy.

### 2.3. Late-treatment group

In the late-treatment group, every subject with serum HBV DNA  $\geq 1 \times 10^6$  IU/mL was given medical counsel and told the potential benefits and side effects of telbivudine treatment. The subjects voluntarily decided to participate in this study and gave informed consent.

Subjects voluntarily accepted telbivudine treatment in middle pregnancy (14–28 weeks of gestation), and their infants constituted the late-treatment group ( $n = 135$ ). To evaluate the effect of antiviral drug withdrawal on maternal outcomes, mothers in the late-treatment group were further stratified into termination and nontermination groups, based on the withdrawal of antiviral treatment or not during puerperium. Fifty-five women terminated antiviral therapy during puerperium (the termination group) and 65 did not terminate antiviral therapy until 7 months after labor (the nontermination group). Fifteen subjects in the late-treatment group were excluded from statistical analysis because 9, 1, and 5 terminated antiviral therapy at 3, 4, and 5 months after delivery, respectively.

### 2.4. Control group

The control group ( $n = 316$ ) consisted of subjects with serum HBV DNA  $\geq 1 \times 10^6$  IU/mL who refused telbivudine treatment in middle pregnancy (14–28 weeks of gestation), and their infants.

### 2.5. Telbivudine dosage and follow-up

The telbivudine (Beijing Novartis Pharm, Beijing, China) dosage used in the present study was 600 mg/day. All pregnant women and their infants were followed for 7 months after birth.

## 3. Methods

For subjects in the early-treatment group, HBV serological markers (HBsAg, anti-HBs), HBeAg, anti-HBe, and anti-HBc), HBV DNA, and liver and kidney function were assayed at the first prenatal examination, within 24 hours of delivery, and 7 months after delivery. For subjects in the late-treatment group the HBV serological markers and liver and kidney function were assayed at

the first prenatal examination, and HBV DNA was assayed after confirmation of HBsAg positivity. These were reassayed within 24 hours of delivery, and 7 months after delivery.

Enzyme-linked immunosorbent assay (ELISA) kits for the HBV serological markers were purchased from Zhongshan Bioengineering, Zhongshan, China. ELISA was performed in accordance with the manufacturer's protocol.

HBV DNA levels were assessed via real-time quantitative polymerase chain reaction using a specific kit (Daan Gene, Guangzhou, China) and amplification of HBV DNA was performed in accordance with the manufacturer's instructions. HBV DNA  $\geq 100$  IU/mL was considered a positive result and HBV DNA  $< 100$  IU/mL was considered negative.

All newborns received 200 IU hepatitis B immunoglobulin (Sichuan Yuanda Shuyang Pharmaceutical, Chengdu, China) within 6 hours of birth. In addition, all newborns received 10  $\mu$ g of yeast-derived recombinant HBV vaccine (HBVac, Beijing Tiantan Biological Products, Beijing, China) at 0, 1, and 6 months after birth. Serum samples of femoral venous blood were obtained from newborns prior to the combined vaccination and at 7 months of age. Serum samples of elbow venous blood were collected from each pregnant woman before delivery and 7 months after delivery. Vaccination failure of newborns was defined as HBsAg and/or HBV DNA positivity from birth to 7 months. Vaccination success was considered negative HBsAg and positive anti-HBs in infants at 7 months of age after passive-positive immunoprophylaxis.

Alanine transaminase (ALT) in pregnant women was assayed using the pyruvate oxidase method at enrollment, within 24 hours before labor, and 7 months after delivery. ALT  $< 40$  U/L was considered normal.

### 3.1. Apgar score assay

Infants were given an Apgar score as described in a previous report,<sup>[21]</sup> briefly as follows. Skin color: 2, ruddy all over the body; 1, ruddy body and blue limbs; and 0, blue or pale skin. Heart rate: 2,  $> 100$  BPM; 1,  $< 100$  BPM; 0, no BPM. Breathing: 2, regular breathing and crying; 1, slow and irregular breathing; 0, no breathing. Muscle tone: 2, active motion; 1, some flexing of arms and legs; 0, limp. Reflex response: 2, loud cries; 1, grimace; 0, none.

An Apgar score of 8 to 10 points was normal for newborns; 4 to 7 points indicated mild asphyxia; and 0 to 3 points was considered severe asphyxia.

### 3.2. Statistical analysis

Statistical analyses were performed using SPSS software (Version 17.0; SPSS Inc, Chicago, IL). Numerical data were analyzed using one-way analysis of variance and rank-sum tests. Qualitative data was analyzed using  $\chi^2$  and Fisher exact tests.  $P < 0.05$  was considered statistically significant.

## 4. Results

### 4.1. Subjects comprising the final analysis

Initially, 37, 145, and 334 subjects were enrolled in the early-treatment, late-treatment, and control groups, respectively. Thirty-one subjects were lost during the 7-month follow-up after birth because of change of contact telephone number, change of residence, mother's refusal to test baby, or failure to obtain a sufficient blood sample from the infant.

In the final analysis, there were 34 mothers with their 34 infants in the early-treatment group, 135 mothers with their 137 infants (2 mothers with twins) in the late-treatment group, and 316 mothers with their 320 infants in the control group (4 mothers with twins; Table 1). The 3 groups were statistically similar in age, gravidity, parity, rates of threatened abortion, and rates of threatened premature labor ( $P > 0.05$ ; Table 1). However, there were significant differences in the rates of HBeAg positivity, HBV DNA load, and ALT among the 3 groups ( $P < 0.05$ ; Table 1).

### 4.2. HBV and liver and kidney function parameters

At enrollment, the rate of HBeAg positivity (64.70%) and HBV DNA levels (2 [1.82–6.99]  $\log_{10}$  IU/mL) of pregnant women in the early-treatment group were significantly lower than that of the late-treatment group (90.37% and 7.69 [6.05–8.98]  $\log_{10}$  IU/mL) and the control group (85.44% and 7.67 [6.0–8.91]  $\log_{10}$  IU/mL), while the late-treatment and control groups were similar (Table 2). The ALT of the late-treatment group (37 U/L) was significantly higher than that of the early-treatment (18 U/L) and

**Table 1**  
General features of mothers in the 3 groups at enrolment.

	Early treatment	Late treatment	Control	$\chi^2$	P
Subjects, n	34	135	316	—	—
Age, median (range), y	29 (23–39)	29 (20–38)	28 (20–41)	5.386	0.068*
Gravidity, median (range), n	1.5 (1–5)	1 (1–5)	2 (1–8)	0.938	0.626*
Parity, median (range), n	1 (1–2)	1 (1–3)	1 (1–4)	3.623	0.163*
Threatened abortion, n (%)	6 (17.64)	20 (14.81)	38 (12.03)	1.275	0.529†
Threatened premature labor, n (%)	0 (0)	2 (1.48)	8 (2.53)	1.286	0.526†
HBeAg <sup>+</sup> , n (%)	22 (64.70)	122 (90.37)	270 (85.44)	14.321	0.001†
HBV DNA, median (range), $\log_{10}$ IU/mL	2 (1.82–6.99)	7.69 (6.05–8.98)	7.67 (6–8.91)	90.221	$< 0.001$ *
ALT, median (range), U/L	18 (9–500)	37 (6–697)	22 (5–623)	44.785	$< 0.001$ *
CK, median (range), U/L	70.5 (28–625)	49 (20–380)	50 (17–261)	5.620	0.060*
BUN, median (range), $\mu$ mol/L	4.16 (1.09–5.97)	2.95 (1.43–7.04)	2.96 (1.38–5.80)	1.910	0.385*
Cre, median (range), $\mu$ mol/L creatinine	46 (33.9–68)	47 (32.8–139.7)	47 (34.5–72)	0.690	0.708*

ALT = alanine transaminase, BUN = blood urea nitrogen, CK = creatine kinase, Cre = creatinine, HBeAg = hepatitis Be-antigen, HBV = hepatitis B virus.

\*Kruskal–Wallis rank-sum test.

†  $\chi^2$  test.

**Table 2****The comparisons of HBeAg positivity rate, HBV DNA level, and ALT in 3 groups at enrolment.**

Group	n	HBeAg+ N (%)	$\chi^2$	P	HBV DNA, median (range), log <sub>10</sub> IU/mL	Z*	P	ALT, median (range), U/L	Z*	P
Early treatment	34	22 (64.70)	14.193	<0.001 <sup>†</sup>	2 (1.82–6.99)	-8.827	<0.001 <sup>†</sup>	18 (9–500)	-4.011	<0.001 <sup>†</sup>
Late treatment	135	122 (90.37)	9.548	0.002 <sup>‡</sup>	7.69 (6.05–8.98)	-9.320	<0.001 <sup>‡</sup>	37 (6–697)	-1.034	0.301 <sup>‡</sup>
Control	316	270 (85.44)	2.020	0.155 <sup>§</sup>	7.67 (6–8.91)	-0.588	0.557 <sup>§</sup>	22 (5–623)	-6.374	<0.001 <sup>§</sup>

ALT = alanine transaminase, HBeAg = hepatitis Be-antigen, HBV = hepatitis B virus.

\* Rank test for 2 independent samples.

<sup>†</sup> Comparison between early-treatment and late-treatment groups.<sup>‡</sup> Comparison between early-treatment and control groups.<sup>§</sup> Comparison between late-treatment and control groups.

control (22 U/L) groups; the early-treatment and control groups were similar (Table 2). Creatine phosphate kinase (CK), blood urea nitrogen (BUN), and creatine (Cre) were statistically comparable among 3 groups.

The percentages of HBsAg- and/or HBV DNA-positive infants at birth in the early-treatment, late-treatment, and control groups were 2.94% (1/34), 2.19% (3/137), and 12.19% (39/320), respectively. Forty-three infants (1 in the early-treatment, 3 in the late-treatment, and 39 in the control group) were positive for HBsAg or HBV DNA at birth, and all of their mothers had a high serum HBV DNA level ( $\geq 1.0 \times 10^6$  IU/mL; Table 3).

At 7 months after birth, no infant in the early-treatment or late-treatment groups was positive for HBsAg or HBV DNA, and therefore the rate of MTCT was nil (Table 4). However, 15 infants in the control group were positive for HBsAg or HBV DNA, and the rate of MTCT was 4.69% (15/320). The MTCT of the control group was statistically higher than that of the late-treatment group, but a statistical difference between the control and early-treatment groups could not be shown.

At the 7-month follow-up, the rates of infants positive for anti-HBs among the 3 groups were statistically similar (Table 4). Specifically, these rates were 91.18% (31/34), 95.62% (131/137), and 89.06% (285/320) for the early-treatment, late-treatment, and control groups, respectively.

To monitor the changes in liver and kidney function and HBV DNA levels in pregnant women after antiviral therapy, we assayed the ALT, CK, BUN, Cre, and HBV DNA levels in pregnant women at enrollment and within 24 hours of labor (Table 5). In the early-treatment group, the HBV DNA levels just prior to labor were markedly lower than at enrollment ( $P < 0.05$ ) and the CK levels before labor were markedly higher than at enrollment ( $P < 0.05$ ), whereas there were no significant differences in ALT, BUN, Cre levels or rates of HBV DNA positivity between the enrollment and imminent labor measurements. In the late-treatment group, the ALT and HBV DNA levels, and rate of HBV DNA positivity, before labor were significantly lower than at enrollment and CK levels before labor were markedly higher than at enrollment. There were no significant differences in BUN and Cre levels between the enrollment and imminent labor measurements.

#### 4.3. Effects of antiviral therapy termination on maternal outcomes

At 7 months after labor, no mothers in the early-treatment group had discontinued antiviral therapy. Among the 135 mothers in the late-treatment group, 55 terminated antiviral therapy during puerperium (the termination group), having received a mean of 80 days of antiviral therapy (range, 32–169 days), whereas 65 did

not terminate antiviral therapy until 7 months after labor (the nontermination group). Fifteen subjects in the late-treatment group were excluded from statistical analysis because 9, 1, and 5 terminated antiviral therapy at 3, 4, and 5 months after delivery, respectively. Prior to labor (within 24 hours), the termination and nontermination groups were statistically similar for rates of positive HBeAg, HBV DNA, or levels of ALT or HBV DNA (Table 6). However, at 7 months after delivery, the rates of positive HBeAg, HBV DNA, or the levels of HBV DNA of the termination group were significantly higher than that of the nontermination group; ALT levels remained similar.

#### 4.4. Adverse effects associated with antiviral therapy in mothers

There were no significant differences among the 3 groups with regard to rates of gestational diabetes mellitus, oligoamnios, hypertensive disorder complicating pregnancy, premature rupture of membranes, postpartum hemorrhage, or Cesarean section (Table 7).

None of the patients in the early-treatment and late-treatment groups had an adverse outcome such as rhabdomyolysis or myodynia.

#### 4.5. Effects of antiviral therapy on infants

Among the infants of the 3 groups, there were no significant differences in birth weight, Apgar score at 1 minute or 5 minutes, or weight and height at 7 months of age (Table 8). One infant in the late-treatment group presented with congenital laryngeal stridor and was self-healed at 7 months of age; rickets was seen in 1 infant at 7 months of age. One infant in the control group suffered pneumonia and another one infant had pericardial effusion at 7 months of age. The rest of the infants were healthy.

There were no significant differences in rates of premature birth, low birth weight, giant baby, neonatal asphyxia, neonatal defect, or neonatal hyperbilirubinemia among the infants of the 3 groups (Table 9).

## 5. Discussion

The timing of intrauterine infection during pregnancy, and appropriate initiation of telbivudine treatment during pregnancy, has not been determined definitively. In the present study, we investigated the maternal and infant outcomes of telbivudine treatment in HBV-infected women, beginning at different gestational stages of pregnancy. The results showed that telbivudine treatment during pregnancy could significantly reduce serum HBV DNA levels, and no infant was infected with



**Table 3**  
**HBV serological markers in 43 infants with HBsAg and/or HBVDNA positivity at birth.**

Group	No.	Mother		Infant at birth					Infant at 7 months						
		HBsAg	HBV DNA*	HBsAg	Anti-HBs	HBsAg	Anti-HBe	Anti-HBc	HBV DNA*	HBsAg	Anti-HBs	HBsAg	Anti-HBe	Anti-HBc	HBV DNA*
Early treatment	1	-	<100	+	-	-	+	+	<100	-	+	-	-	+	<100
Late treatment	2	+	9.49 × 10 <sup>6</sup>	+	-	+	-	+	<100	-	+	-	-	+	<100
	3	+	2.65 × 10 <sup>8</sup>	+	-	+	-	+	<100	-	+	-	-	+	<100
	4	+	2.66 × 10 <sup>8</sup>	+	-	+	-	+	<100	-	+	-	-	-	<100
Control	5	+	4.50 × 10 <sup>6</sup>	-	-	-	+	+	9.18 × 10 <sup>2</sup>	-	-	-	-	-	<100
	6	+	1.65 × 10 <sup>8</sup>	+	-	+	-	+	3.53 × 10 <sup>4</sup>	+	-	+	-	+	1.53 × 10 <sup>2</sup>
	7	+	4.00 × 10 <sup>8</sup>	+	-	+	-	+	2.88 × 10 <sup>3</sup>	+	-	+	-	+	3.66 × 10 <sup>5</sup>
	8	+	3.03 × 10 <sup>8</sup>	+	-	+	-	+	5.46 × 10 <sup>3</sup>	+	-	+	-	+	7.74 × 10 <sup>7</sup>
	9	+	5.24 × 10 <sup>7</sup>	+	-	-	+	+	2.95 × 10 <sup>4</sup>	-	+	-	-	-	<100
	10	+	1.06 × 10 <sup>8</sup>	+	-	+	-	+	5.42 × 10 <sup>4</sup>	+	-	+	-	+	2.38 × 10 <sup>8</sup>
	11	+	1.41 × 10 <sup>8</sup>	+	-	+	-	+	2.79 × 10 <sup>7</sup>	+	-	+	-	+	1.95 × 10 <sup>7</sup>
	12	+	1.06 × 10 <sup>7</sup>	-	-	+	-	+	1.94 × 10 <sup>3</sup>	-	+	-	-	-	<100
	13	+	2.94 × 10 <sup>8</sup>	-	-	+	-	+	7.02 × 10 <sup>2</sup>	-	+	-	-	-	<100
	14	+	3.02 × 10 <sup>8</sup>	+	-	+	-	+	8.21 × 10 <sup>2</sup>	+	-	+	-	+	1.85 × 10 <sup>5</sup>
	15	+	1.64 × 10 <sup>8</sup>	+	-	-	+	+	<100	-	+	-	+	+	<100
	16	-	2.77 × 10 <sup>6</sup>	+	-	-	+	+	<100	-	+	-	-	+	<100
	17	+	2.82 × 10 <sup>8</sup>	+	-	+	-	+	1.46 × 10 <sup>5</sup>	+	-	+	-	+	4.06 × 10 <sup>6</sup>
	18	+	5.11 × 10 <sup>8</sup>	+	-	+	-	+	<100	-	-	-	-	-	<100
	19	+	2.13 × 10 <sup>8</sup>	+	-	+	-	+	<100	-	+	-	+	+	<100
	20	+	1.04 × 10 <sup>8</sup>	+	-	+	-	+	<100	+	-	+	-	+	1.87 × 10 <sup>4</sup>
	21	+	4.09 × 10 <sup>8</sup>	+	-	+	-	+	<100	+	-	-	+	+	<100
	22	+	5.18 × 10 <sup>8</sup>	+	-	+	-	+	<100	-	+	-	-	-	<100
	23	+	1.37 × 10 <sup>6</sup>	-	-	+	-	+	5.23 × 10 <sup>3</sup>	-	+	-	-	-	<100
	24	+	1.44 × 10 <sup>8</sup>	-	+	-	+	+	<100	-	+	-	-	-	<100
	25	+	2.12 × 10 <sup>7</sup>	+	-	+	-	+	<100	-	+	-	-	-	<100
	26	+	5.62 × 10 <sup>8</sup>	+	-	+	-	+	1.32 × 10 <sup>4</sup>	+	-	+	-	+	1.05 × 10 <sup>8</sup>
	27	+	9.43 × 10 <sup>7</sup>	+	-	+	-	+	<100	-	+	-	-	-	<100
	28	+	2.17 × 10 <sup>8</sup>	+	-	+	-	+	3.30 × 10 <sup>4</sup>	+	-	+	-	+	1.00 × 10 <sup>4</sup>
	29	+	9.07 × 10 <sup>7</sup>	+	-	+	-	+	3.05 × 10 <sup>4</sup>	+	-	+	-	+	9.03 × 10 <sup>7</sup>
	30	+	5.26 × 10 <sup>8</sup>	+	-	+	-	+	3.20 × 10 <sup>3</sup>	+	-	-	+	+	<100
	31	+	1.11 × 10 <sup>8</sup>	+	-	+	-	+	6.08 × 10 <sup>3</sup>	-	+	-	-	+	<100
	32	+	3.18 × 10 <sup>7</sup>	+	-	+	-	+	2.08 × 10 <sup>6</sup>	+	-	+	-	+	5.30 × 10 <sup>7</sup>
	33	+	2.76 × 10 <sup>8</sup>	+	-	+	-	+	<100	-	+	-	-	-	<100
	34	+	2.79 × 10 <sup>8</sup>	+	-	+	-	+	1.11 × 10 <sup>6</sup>	+	-	+	-	+	3.10 × 10 <sup>8</sup>
	35	+	1.30 × 10 <sup>7</sup>	+	-	+	-	+	<100	-	+	-	-	+	<100
	36	+	3.13 × 10 <sup>8</sup>	+	-	+	-	+	<100	-	+	-	-	-	<100
	37	+	1.15 × 10 <sup>7</sup>	+	-	+	-	+	1.23 × 10 <sup>3</sup>	-	+	-	-	-	<100
	38	+	3.67 × 10 <sup>7</sup>	-	-	+	-	+	5.67 × 10 <sup>2</sup>	-	+	-	-	-	<100
	39	+	2.14 × 10 <sup>8</sup>	+	-	+	-	+	<100	-	-	-	-	-	<100
	40	+	1.30 × 10 <sup>7</sup>	+	-	-	+	+	<100	-	+	-	-	-	<100
	41	+	9.95 × 10 <sup>7</sup>	+	-	+	-	+	<100	-	+	-	-	-	<100
	42	+	8.69 × 10 <sup>7</sup>	+	-	+	-	+	<100	-	-	-	-	-	<100
	43	+	1.94 × 10 <sup>7</sup>	-	-	+	-	+	1.75 × 10 <sup>3</sup>	-	+	-	-	-	<100

HBsAg=hepatitis Be-antigen, HBsAg=hepatitis B surface antigen, HBV=hepatitis B virus.  
 \*IU/mL.

HBV during telbivudine treatment lasting 7 months after birth. Initiation of telbivudine during middle or late pregnancy caused a marked decrease of MTCT. The rate of MTCT in women who began telbivudine therapy before or during early pregnancy was nil, but statistically similar to that of the control group (without antiviral treatment), probably because of the small sample size (only 34 infants). We also noted that 43 infants were HBsAg and/or HBV DNA positive at birth, and most of their mothers had a high serum HBV DNA level (≥1.0 × 10<sup>6</sup> IU/mL). Among above 43 infants, only 1 case was from early-treatment group and the mother's HBV DNA was less than 100IU/mL. At month 7 after birth the infants' HBsAg become negative in both early-treatment and late-treatment groups, indicating no infant was infected with HBV. In contrast, 15 infants (4.65%) in control group were HBsAg and/or HBV DNA positive at month 7 after birth, with a

significant higher rate of MTCT compared with late-treatment group. We noted that there was no significant difference in the rate of MTCT between control and early-treatment groups, perhaps because of small sample size in the early-treatment group. In the early-treatment group, the antiviral treatment was administered before pregnant or in early pregnancy, leading to the decrease in HBV DNA (2 (1.82–6.99) log<sub>10</sub> IU/mL) at enrollment, with a significant difference in HBV DNA compared with the late-treatment group. But the HBV DNA in the early-treatment and late-treatment groups decreased after antiviral treatment and no 1 case was infected with HBV. These results clearly indicate that antiviral therapy during pregnancy is necessary to reduce HBV DNA levels and decrease the rate of MTCT of HBV. A further study with a larger sample size is required to elucidate the effect on MTCT of HBV of

**Table 4****Infant rates of MTCT and vaccination success among the 3 groups, n (%).**

		Early treatment	Late treatment	Control
Subjects, n		34	137	320
HBsAg <sup>+</sup> and/or HBV DNA <sup>+</sup>	At birth	1 (2.94)	3 (2.19)	39 (12.19)
	7 mo	0 (0)	0 (0)	15 (4.69)
	MTCT	0 (0)	0 (0)	15 (4.69)
	$\chi^2$	—	—	8.268
	P	0.378*	0.007 <sup>†</sup>	0.016 <sup>‡</sup>
Anti-HBs <sup>+</sup>	At birth	0 (0)	4 (2.92)	6 (1.88)
	7 mo	31 (91.18)	131 (95.62)	285 (89.06)
	Vaccination success	31 (91.18)	131 (95.62)	285 (89.06)
	$\chi^2$	—	—	5.058
	P	—	—	0.080 <sup>‡</sup>

Fisher exact test.

ALT = alanine transaminase, HBeAg = hepatitis Be-antigen, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, MTCT, mother-to-child transmission.

\* Comparison between early-treatment and control groups.

<sup>†</sup> Comparison between late-treatment and control groups.<sup>‡</sup> Comparison between 3 groups.

initiation of telbivudine treatment specifically before or during early pregnancy.

Nucleoside analogues generally inhibit HBV DNA synthesis and do not completely eliminate the virus. HBV is likely to return to the original virus level or rise even higher, which may induce severe liver dysfunction after discontinuation of treatment. In addition, long-term treatment may cause virus mutation, drug resistance, and other side effects.<sup>[22]</sup> HBV infection in pregnant women could increase the risk of pregnancy complications including gestational diabetes, hypertension, and postpartum hemorrhage. Nucleoside analogue treatment could decrease HBV DNA levels and reduce hepatitis activity, stabilizing liver function. Therefore, the decision to use antiviral drugs during pregnancy must balance the risks and benefits to both the mother and fetus. In the present study, the treatment (telbivudine) and control groups were similar in rates of gestational diabetes mellitus, hypertensive disorder complicating pregnancy, premature rupture of membranes, postpartum hemorrhage, and Cesarean section. This indicates that telbivudine treatment for HBV during pregnancy did not increase the rates of adverse outcomes of pregnancy and is safe for mothers. But nucleoside analogues could decrease the mitochondrial DNA level in cells, leading to adverse outcomes in mitochondrial-rich organs including kidneys and muscles.

Telbivudine carries a potential risk of myopathy and myositis.<sup>[23]</sup> CK is an enzyme involved in metabolism, mainly located in skeletal and cardiac muscles, which increases

significantly in response to muscle damage. Thus, elevated CK may indicate muscle damage. However, CK also increases after strenuous exercise, and therefore is not specific to muscle damage. Nucleoside drug treatment can rapidly increase CK levels by many times, leading to rhabdomyolysis, myodynia, and leg weakness, and should be continued with close monitoring if CK is only moderately elevated and there are no obvious muscle symptoms. In the present study, BUN, Cre, and CK were comparable among the 3 treatment groups at enrollment, and there were no significant differences in BUN or Cre levels before and after telbivudine treatment. Although the CK value before labor was higher than at enrollment, none of the patients had rhabdomyolysis, myodynia, or leg weakness. These data indicated that telbivudine treatment was safe for pregnant women.

The safety of the fetus when using antiviral therapy during pregnancy in HBV-infected pregnant women is an important concern. The current available data on the safety of antiviral therapy during pregnancy is mostly from trials evaluating the use of antiviral therapy in the prevention of MTCT.<sup>[24]</sup> Antiviral drugs against HBV are classified into 5 categories (A-D, X) based on safety data for pregnancy published by the United States Food and Drug Administration.<sup>[22]</sup> In general, drugs in pregnancy risk category B are safe to use during pregnancy, and these include telbivudine and tenofovir. All other antiviral drugs are classified as FDA pregnancy risk category C and are not recommended for use during pregnancy.

**Table 5****ALT, CK, BUN, Cre, and HBV DNA in pregnant women in the early- and late-treatment groups\*.**

	Early treatment, n=34				Late treatment, n=135			
	Enrollment	Before labor	$\chi^2$	P	Enrollment	Before labor	$\chi^2$	P
ALT, U/L	18 (9–500)	16.5 (3.5–41)	−1.339 <sup>†</sup>	0.181	37 (6–697)	23 (2–498)	−5.919 <sup>†</sup>	<0.001
CK, U/L	70.5 (28–625)	126 (42–256)	−2.991 <sup>†</sup>	0.003	49 (20–380)	71.5 (17–526)	−3.790 <sup>†</sup>	<0.001
BUN, $\mu$ mol/L	4.16 (1.09–5.97)	3.35 (2.08–5.13)	−0.353 <sup>†</sup>	0.724	2.95 (1.43–7.04)	3.23 (1.04–6.73)	−1.797 <sup>†</sup>	0.072
Cre, $\mu$ mol/L	46 (33.9–68)	52.1 (32–61.5)	−1.862 <sup>†</sup>	0.063	47 (32.8–139.7)	51 (30.8–128.0)	−1.507 <sup>†</sup>	0.132
HBV DNA, log <sub>10</sub> IU/mL	2 (1.82–6.99)	2 (1.77–4.90)	−2.110 <sup>†</sup>	0.035	7.69 (6.05–8.98)	3.70 (2.00–7.73)	−14.042 <sup>†</sup>	<0.001
HBV DNA <sup>+</sup> , n (%)	12 (35.29)	6 (17.65)	2.720	0.099	135 (100)	102 (75.56)	37.595	<0.001

ALT = alanine transaminase, BUN = blood urea nitrogen, CK = creatine kinase, Cre = creatinine, HBV = hepatitis B virus.

\* Median (range), unless indicated otherwise.

<sup>†</sup> Z value in Kruskal–Wallis rank-sum test.

**Table 6****Effect of antiviral therapy termination during puerperium on HBeAg, HBV DNA, and ALT levels in late-treatment group mothers within 24 h before labor and 7 mo after delivery.**

Group	n	HBeAg+, n (%)		HBV DNA+, n (%)		HBV DNA, log <sub>10</sub> IU/mL*		ALT, U/L*	
		Before	7 mo	Before	7 mo	Before	7 mo	Before	7 mo
Termination	55	48 (87.27)	51 (92.73)	36 (65.45)	48 (87.27)	3.85 (2–6.87)	6.38 (1.79–8.55)	24 (9–116)	26.5 (11–588)
Non-termination	65	57 (87.69)	41 (63.08)	41 (74.55)	31 (47.69)	3.16 (2–7.73)	2 (1.31–8.37)	25 (2–498)	27 (5–60)
$\chi^2$ or Z	—	0.005	14.641	0.073	20.749	–1.791	–6.010	–0.661	–0.291
P	—	0.945†	<0.001†	0.787†	<0.001†	0.073‡	<0.001‡	0.508‡	0.771‡

ALT = alanine transaminase, HBeAg = hepatitis Be-antigen, HBV = hepatitis B virus.

\* Median (range).

†  $\chi^2$  test.

‡ Kruskal–Wallis rank-sum test.

Studies have shown that the use of tenofovir and telbivudine during pregnancy is safe for neonates and does not increase the incidence of congenital malformation.<sup>[25,26]</sup> Another study with 362 pregnant women reported that use of telbivudine during middle and late pregnancy was safe and effective, without associated congenital malformations.<sup>[27]</sup> However, in these studies antiviral treatment was initiated during middle or late pregnancy, and there is no confirmed safety data on antiviral treatment initiated during early pregnancy. In fact, in some women with high HBV DNA load and abnormal liver function, antiviral treatment against HBV frequently was initiated during early pregnancy to improve liver function after invalid routine liver protection therapy.

Some HBV-infected women conceive while undergoing anti-HBV treatment. If withdrawal of the treatment is rushed, HBV will return to the original level or higher and active hepatitis can even be induced, resulting in severe liver dysfunction.<sup>[11]</sup> On the other hand, if the treatment is continued there is the potential to affect adversely the outcome of pregnancy, fetal prognosis, birth defects, or the long-term safety of the infant.

Most current studies focus on birth defects, and not on the long-term growth and development of infants. In the present study, we investigated the outcomes of infants at birth and at 7 months after birth, after antiviral treatment of the mother during pregnancy. Compared with the untreated control group, antiviral therapy was not associated with any significant effect on neonatal outcome, birth weight, Apgar score, or rate of birth defects at birth. At the 7-month follow-up, no adverse effects on infant height or weight or serious complications were observed. These data indicate that treatment with telbivudine of mothers during pregnancy, even when begun in early pregnancy, did not have adverse effects on the health of the newborn or 7-month-old infant.

The objective of antiviral therapy in HBV-infected pregnant women is to decrease serum HBV DNA levels and prevent MTCT

of HBV. However, antiviral treatment continued postpartum may increase the likelihood of drug resistance and adverse reactions, as well as affect breastfeeding. Current guidelines concerning anti-HBV therapy lack detailed suggestions; most recommend long-term oral antiviral drugs. In 2012, the European Association for the Study of the Liver<sup>[28]</sup> recommended the termination of antiviral drugs within 3 months postpartum, if its purpose was only to block MTCT of HBV. In the present study, increased ALT is known to be associated with hepatitis flare-up in HBV-infected women.<sup>[29,30]</sup> Therefore, ALT levels should be monitored to evaluate liver function after discontinuation of antiviral treatment.

Most of the relevant studies have focused on the effect of antiviral treatment for reducing MTCT of HBV; very few have investigated the rate of infant vaccination success after passive and positive immunoprophylaxis, and conclusions were not consistent. Han et al<sup>[31]</sup> reported that maternal antiviral treatment during the second and third trimesters could increase the rate of vaccination success of the infant at 7 months of age, based on lower infant serum anti-HB antibody levels. However, another study showed that maternal antiviral treatment during the second and third trimesters had no effect on the production of anti-HBs in infants.<sup>[13]</sup> Our present results show that maternal anti-HBV treatment, starting from the first or second trimester, did not affect the production of anti-HBs at 7 months of follow-up and had no effect on the rate of vaccination success after combined immunoprophylaxis.

In conclusion, in the present study, telbivudine treatment of HBV-infected pregnant women during the second or third trimester was associated with a significant decrease in serum HBV DNA levels and a lower rate of MTCT of HBV, relative to the untreated control. This treatment did not affect outcomes of pregnancy and did not have adverse effects on neonatal outcomes at birth or development at 7 months of age. Similarly, initiation of

**Table 7****Adverse outcomes in mothers, n (%).**

	Early treatment	Late treatment	Control	$\chi^2$	P
Subjects, n	34	135	316	—	—
Gestational diabetes mellitus	8 (23.52)	26 (19.26)	40 (12.66)	5.123	0.077
Oligohydramnios	3 (8.82)	7 (5.19)	20 (6.33)	0.652	0.722
Hypertensive disorder complicating pregnancy	1 (2.94)	4 (2.96)	8 (2.53)	0.077	0.962
Premature rupture of membranes	6 (17.64)	26 (19.26)	54 (17.09)	0.306	0.858
Postpartum hemorrhage	2 (5.88)	3 (2.22)	9 (2.85)	1.296	0.523
Caesarean section	15 (44.11)	61 (45.18)	125 (39.56)	1.342	0.511

**Table 8****General features of infants, median (range).**

	n	Birth			7 Mo	
		Weight, kg	Apgar score 1 <sup>/</sup>	Apgar score 5 <sup>/</sup>	Weight, kg	Height, cm
Early-treatment	34	3.2 (2.45–4.0)	10 (10–10)	10 (10–10)	8.48 (6.7–11.5)	70.00 (65–80)
Late-treatment	137	3.1 (1.7–4.25)	10 (7–10)	10 (8–10)	8.20 (6.5–10.5)	70.50 (65–76)
Control	320	3.1 (1.0–4.10)	10 (2–10)	10 (6–10)	8.05 (5–11)	70.00 (60.5–76)
$\chi^2$	—	3.331	3.329	1.648	5.421	1.363
P	—	0.189	0.189	0.439	0.066	0.506

Kruskal–Wallis rank-sum test.

**Table 9****Adverse outcomes in infants among 3 groups, n (%).**

	n	Premature	Low birth weight	Giant baby	Asphyxia	Deformity	Hyperbilirubinemia
Early-treatment	34	2 (5.88)	1 (2.94)	1 (2.94)	0 (0)	0 (0)	8 (23.53)
Late-treatment	137	12 (8.76)	7 (5.11)	3 (2.19)	2 (1.46)	1 (0.73)	16 (11.68)
Control	320	28 (8.75)	15 (4.69)	6 (1.88)	9 (2.81)	0 (0)	32 (10.00)
$\chi^2$	—	0.333	0.287	0.197	1.639	2.589	5.582
P	—	0.846	0.866	0.906	0.441	0.274	0.061

telbivudine treatment during early pregnancy did not adversely affect the outcomes of mothers or infants. Nevertheless, telbivudine treatment during pregnancy did not increase the rate of vaccination success in infants with combined immunoprophylaxis. Telbivudine appears to be safe and feasible in patients who underwent puerperium withdrawal of antiviral therapy after short-term use during pregnancy, based on relatively stable liver function. We recognize that this study has limited statistical power due to the relatively small size of the groups, which may affect our conclusion. Therefore, a further study with a larger population and longer research period is required to confirm the effects of antiviral treatment against HBV during pregnancy on maternal and infant outcomes, especially during early pregnancy.

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