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ORIGINAL ARTICLE

Safety and efficacy of lamivudine or telbivudine started in early pregnancy for mothers with active chronic hepatitis B

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Abstract

Background Few data exist regarding use of nucleos(t)ide analogs started in early pregnancy for mothers with active chronic hepatitis B (CHB). We assessed the safety and efficacy of lamivudine/telbivudine initiated in the first trimester versus no treatment in mothers with active CHB.

Methods We retrospectively enrolled 94 mothers newly diagnosed with active CHB in the first trimester of pregnancy. Patients with or without antiviral therapy were followed until postpartum week 28. All newborns received immunoprophylaxis. The primary endpoint was the safety of mothers and infants. The secondary endpoints were hepatitis B virus (HBV) DNA suppression and mother-to-child transmission (MTCT) rate.

Results Fifty-nine of the 94 mothers initiated lamivudine/telbivudine (27/32) in the first trimester of pregnancy; 35 received no treatment. At delivery, the viral load reduction was similar between lamivudine and telbivudine. Early initiation of lamivudine/telbivudine significantly increased the proportion of mothers achieving HBV DNA $<10^6$ copies/ml compared with those with no treatment (100 versus 42.42 %, $p < 0.001$). At postpartum week 28, the MTCT rate was significant lower in the treated group than in the control group (0/61 or 0 versus 4/34 or 11.76 %, $p = 0.028$). Lamivudine and telbivudine were well tolerated in the mothers except mild creatine kinase (CK) elevation. There existed no differences in gestational age, infant length and weight, Apgar score, adverse events, or birth defect rates between infants from treated and untreated mothers.

Conclusions Treatment with lamivudine or telbivudine for active CHB in early pregnancy appears to be safe and effective for controlling maternal disease as well as interrupting MTCT.

Keywords Chronic hepatitis B · Lamivudine · Telbivudine · Early · Mother-to-child transmission

Abbreviations

AE	Adverse event
ALT	Alanine transaminase
CHB	Chronic hepatitis B
CK	Creatine kinase
FDA	Food and drug administration
GDM	Gestational diabetes mellitus

Tianyu He, Yuqing Bai, Wei Yi, and Jidong Jia contributed equally to this work.

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HBIG	Hepatitis B immunoglobulin
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HDN	Hemolysis disease of newborn
HIV	Human immunodeficiency virus
LAM	Lamivudine
LBW	Low birth weight
LdT	Telbivudine
LLQ	Lower limit of quantitation
MTCT	Mother-to-child transmission
NA	Neocleos(t)ide analogue
P	Serum phosphorus
PTL	Preterm labor
PCR	Polymerase chain reaction
N/n	Number
SD	Standard deviation
TDF	Tenofovir
ULN	Upper limit of normal

Background

Chronic hepatitis B virus (HBV) infection remains a global health problem. It is estimated that nearly 257 million people worldwide have been chronically infected, 5–20 % of whom may develop cirrhosis, liver failure, and hepatocellular carcinoma (HCC), accounting for 686,000 CHB-related deaths each year [1, 2].

In China and many parts of the world, with the implementation of universal vaccination programs, HBsAg prevalence has declined dramatically [1, 3]. However, a recent epidemiological survey in China [4] showed that HBsAg prevalence among females of child-bearing age remains as high as 5.8 %, implying that a considerable number of females can still potentially transmit HBV to their babies. In addition, HBV infection may adversely affect the process of pregnancy [5].

Currently, HBV vaccination and hepatitis B immunoglobulin (HBIG) are recommended to prevent mother-to-child-transmission (MTCT) in mothers with HBV infection [1]. Undoubtedly, this combined prophylactic approach is highly efficient, but it fails to prevent MTCT in 5–10 % of children born to highly viremic mothers [6]. Besides, a randomized controlled trial conducted by Pande et al. found that HBV vaccine plus HBIG failed to prevent occult HBV infection in newborns [7].

Recently, a number of studies have proved the safety and efficacy of neocleos(t)ide analogues (NAs) initiated in late pregnancy purely for reducing MTCT among mothers with high HBV DNA levels. LAM, which belongs to the Food and Drug Administration (FDA) category C of drugs, has been widely used for pregnant females with CHB due to its satisfactory safety data observed in pregnant females with human immunodeficiency virus (HIV) [8, 9]. A randomized controlled trail conducted by Xu et al. found that LAM initiated in the third trimester of pregnancy for CHB mothers with high viremia could effectively reduce MTCT rates, without significant adverse events occurring [10]. Besides, a retrospective cohort study conducted by Pan et al. enrolled highly viremic mothers initiating LAM in either the second or third trimester of pregnancy. They demonstrated that LAM could reduce the MTCT rate safely and effectively; no significant differences in maternal or infant outcomes were observed between the groups initiating LAM in second versus third trimester [11]. In addition, three nonrandomized prospective studies from China supported the safety and efficacy of LdT initiated in the second or third trimester of pregnancy for reducing MTCT [12–14]. Recently, a multicenter, randomized controlled trail conducted by Pan et al. demonstrated that TDF initiated at 30–32 weeks of gestation for mothers with HBV DNA above 10^6 copies/ml could reduce MTCT rates both safely and effectively [15].

Unfortunately, mothers with CHB still present a unique dilemma to clinicians, since the management approach for this population is based on not only reduction of MTCT but also controlling progression of maternal disease, especially when dealing with mothers with active CHB in early pregnancy. Unfortunately, clinical data on use of NAs in early pregnancy for controlling maternal disease and interrupting MTCT are still limited. Therefore, we conducted a retrospective study to evaluate the safety and efficacy of lamivudine (LAM) or telbivudine (LdT) initiated in the first trimester versus no treatment in mothers with active CHB.

Methods

Patients and study design

This was a retrospective cohort study which consecutively enrolled females newly diagnosed with CHB through antenatal screening at our hospital between December 2008 and May 2016. The study protocol was approved by the medical ethics committee of Beijing Ditan Hospital, and informed consent was waived (no. BJDTEC-37). The current study complied with the Helsinki Declaration.

Patients with high HBV DNA level (HBV DNA $\geq 10^5$ copies/ml for HBeAg positive or $\geq 10^4$ copies/ml for HBeAg negative) plus elevated ALT level (>2 × ULN) were classified as having active CHB [16]. The exclusion criteria were: in the immune-tolerant phase;

evidence of cirrhosis or renal dysfunction; coinfection with hepatitis C virus, hepatitis delta virus, human immunodeficiency virus, cytomegalovirus, syphilis, or *Toxoplasma gondii*; incomplete clinical data due to poor compliance with regular prenatal care; biological father of the newborn with evidence of CHB infection. The indication for antiviral therapy for enrolled mothers was HBV DNA $\geq 10^5$ copies/ml (HBeAg positive) or $\geq 10^4$ copies/ml (HBeAg negative) plus ALT $>2 \times$ ULN.

Enrolled mothers were divided into treatment and control groups based on their own discretion after explaining the benefits and risks of initiating antiviral therapy in early pregnancy. Maternal data including demographic data, gestational age, duration of NA exposure, serum alanine transaminase (ALT) level, HBV serologic markers, HBV DNA level, pregnancy adverse events, and pregnancy complications, as well as infant data including weight, length, 1-min Apgar score, delivery mode, infant adverse events, birth defect, and serological and virological markers for HBV, were collected retrospectively by retrieving electronic medical records. The mother–infant dyads were followed until the 28th week postpartum.

Immunoprophylaxis schedule and laboratory tests

All infants received 200 IU HBIG (Chengdu Institute of Biological Products, Chengdu, China) intramuscularly within 6 h of birth, plus 10 μg HBV vaccine (Dalian Hissen Biopharm Co., China) within 12 h of birth. The same doses of passive–active immunization were applied at 1 month postpartum, followed by an additional vaccination at 6 months.

All serum samples collected from mothers and/or infants were sent to the central laboratory at Beijing Ditan Hospital for the following tests: HBV DNA level [real-time polymerase chain reaction (PCR), Shanghai Kehua Bioengineering Co. Ltd., Shanghai, China, lower limit of quantitation (LLQ) = 500 copies/ml]; HBV serological markers (chemiluminescent microparticle immunoassay, Architect i2000 analyzer; Abbott Diagnostics, Abbott Park, IL, USA); ALT level (Wako Pure Chemical Industries, Ltd., Japan, ULN <40U/l). Serum creatine kinase (CK) and phosphorus were measured using an automatic analyzer (Hitachi 7600-020, Hitachi High Technologies Co., Tokyo, Japan).

Outcome measures

The primary outcome was safety for mother–infant dyads, which included adverse events, drug tolerability, LAM/LdT resistance, obstetric complications, and birth defects. Birth defect was defined as any major structural malformation in fetus or infant during the prenatal period or postnatal period up to age 28 weeks.

The secondary outcome was LAM/LdT efficacy, which included: (1) the percentage of mothers achieving HBV DNA $<10^6$ copies/ml (partial control) or <500 copies/ml (complete control) prior to delivery; (2) the percentage of mothers with normal ALT level prior to delivery; (3) MTCT rate.

Infants positive for HBV DNA or HBsAg at age 28 weeks were considered to have MTCT. Mothers with induced labor during pregnancy were excluded from efficacy analysis but included in safety analysis.

Statistical methods

Descriptive variables are expressed as mean ± standard deviation (SD) or percentage. Student's t test and chi-square test were applied to compare quantitative and categorical variables, respectively. $p < 0.05$ was considered statistically significant. All data were analyzed using SPSS (version 22.0; IBM Corp Ltd., Armonk, NY).

Results

Study population

There were 856 consecutive mothers who were initially diagnosed with CHB in the first trimester of pregnancy at Beijing Ditan Hospital between December 2008 and May 2016. Of these, 7 mothers who had cirrhosis and 733 mothers who were in the immune-tolerant stage were excluded based on the exclusion criteria. Besides, 22 mothers were further excluded because of incomplete clinical data in the electronic medical record system. Finally, a total of 94 mothers with active CHB were retrospectively enrolled in the present study (Fig. 1).

Fifty-nine mothers who opted for treatment took 100 mg LAM ($n = 27$) or 600 mg LdT ($n = 32$) daily; 35 mothers who opted for no antiviral therapy during pregnancy served as the control group. The mean duration of exposure before delivery was similar between LAM and LdT [27.93 ± 2.01 (SD) versus 27.99 ± 3.27 weeks, $p > 0.05$].

Baseline values in each group were similar, except the cesarean rate (significantly higher in mothers with active CHB treated with LAM) (Table 1). Two mothers in the control group had induced labor at the middle of pregnancy period and were thus excluded from efficacy analysis but included in safety analysis (Fig. 1).

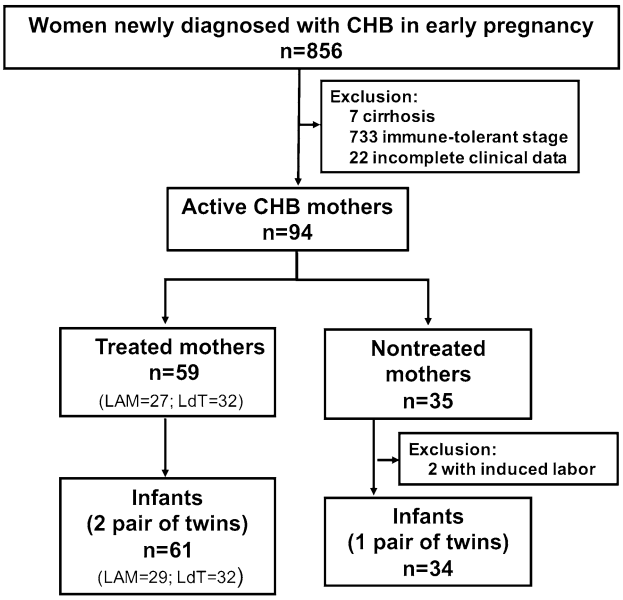

Fig. 1 Flow diagram of subject recruitment. A total of 856 CHB mothers were enrolled in the study. Of these, 762 mothers were excluded based on our exclusion criteria. Therefore, 94 mothers with active CHB with 95 infants were finally selected for statistical analysis. Of note, two mothers with induced labor were further excluded from efficacy analysis but included in safety analysis

Safety information for mothers and fetus

LAM or LdT initiated in early pregnancy was well tolerated. During the study period, no drug discontinuation due to severe adverse events occurred. The incidence of pregnancy complications did not differ significantly between mothers with active CHB treated or untreated (Table 2). Two mothers in the control group terminated the pregnancy in the middle of pregnancy because of fetal pulmonary stenosis and fetal hydrocephalus, respectively. The gestational weeks, used as an indicator of fetal development in our study, were similar between the treated and control groups [38.66 ± 1.43 (SD) versus 38.94 ± 1.22 weeks, $p > 0.05$] (Table 1).

Among treated mothers, serum phosphorus and creatinine levels prior to delivery were similar at enrollment ($p > 0.05$). Before delivery, more mothers in the treated group experienced CK elevation compared with those in the control group (9/59 or 15.3 versus 0/35 or 0 %, $p = 0.037$). However, no clinical manifestations were observed, and all patients' CK levels were within the range of 1.1–2.5 × ULN, corresponding to a grade I AE [17].

Prior to delivery, no viral breakthrough, hepatitis flares (ALT >2 × baseline), or HBeAg loss/seroconversion was observed in the treated groups. The percentage of mothers with normal ALT was significantly higher in the treated group than in the control group (59/59, 100 versus 26/33, 78.79 %, $p = 0.011$) (Table 3). After delivery, all mothers in the treated group continued antiviral therapy and did not give breastfeeding.

In contrast, six mothers in the control group experienced exacerbation of hepatitis and four of them had HBeAg loss/seroconversion; ALT flares resolved without antiviral therapy (taking only hepatoprotectors) (Table 2).

Safety information for infants

Among 95 infants enrolled, there were no significant differences in length, weight, Apgar score (1 min) or cesarean rate between infants from treated and untreated mothers (Table 1). During the follow-up period of up to 28 weeks postpartum, the incidence of adverse events in infants was similar between the two groups (Table 4).

In addition, the birth defect rate was similar between the treated group and control group ($p > 0.05$). Specifically, two cases were observed in the LdT-treated group: one infant with auricular defect, and one infant with ear accessory, whereas three cases were observed in the control group: one infant with ear accessory, one fetus with fetal pulmonary stenosis, and one fetus with fetal hydrocephalus (both fetuses delivered by induced labor in the second trimester of pregnancy). No significant difference in birth defect rate was found between LAM and LdT (0/29 or 0 versus 2/30 or 6.7 %, $p > 0.05$).

Efficacy in mothers

At delivery, significant reduction in HBV DNA viral load (baseline to birth) was observed in mothers with active CHB who were treated but not in those who opted for no antiviral therapy during pregnancy [7.20 ± 0.81 (SD) versus 1.08 ± 1.84 $\log_{10}$ copies/ml, $p < 0.001$], which resulted in a significantly higher proportion of mothers achieving HBV DNA partial control (<10^6 copies/ml) or complete control (<500 copies/ml) in the treated group. No significant difference in reduction of HBV DNA level was found between LAM and LdT [7.01 ± 0.18 (SD) versus 7.37 ± 0.12 $\log_{10}$ copies/ml, $p > 0.05$] (Fig. 2) (Table 3).

Efficacy in infants

All infants enrolled in the study received appropriate passive–active immunoprophylaxis. At birth, a significant higher proportion of infants from untreated mothers were HBsAg positive compared with those from treated mothers (4/61 or 6.56 versus 16/34 or 47.06 %, $p < 0.001$). At age of 28 weeks, four infants (4/34 or 11.76 %) from untreated mothers were still positive for HBsAg, thus being considered to have MTCT; the other infants who were positive for HBsAg at birth responded well to immunoprophylaxis and became HBsAg negative. The MTCT rate was significantly

Table 1 Baseline values for mothers and infants

Variable	LAM	LdT	*p* (LAM versus LdT)	All treated	Control	*p* (all treated versus control)
Mothers, *n*	27	32	–	59	35	–
Age, years	29.19 ± 2.93	29.18 ± 2.89	0.399	29.18 ± 2.90	28.97 ± 3.58	0.747
HBV DNA, $\log_{10}$ copies/ml	7.01 ± 0.91	7.32 ± 0.73	0.088	7.18 ± 0.81	6.95 ± 0.69	0.164
ALT, U/l (normal <40)	188.60 ± 150.31	207.41 ± 142.42	0.892	198.80 ± 146.03	200.95 ± 190.17	0.062
CK, U/l (normal <200)	50.46 ± 20.72	53.88 ± 23.60	0.766	52.31 ± 22.28	48.21 ± 16.58	0.713
Cr, μmol/l (normal <84)	45.52 ± 4.87	44.94 ± 13.23	0.845	45.21 ± 9.40	45.40 ± 7.43	0.862
P, mmol/l (normal 0.81–1.45)	1.14 ± 0.13	1.17 ± 0.15	0.382	1.15 ± 0.14	1.12 ± 0.14	0.193
Duration of exposure, weeks	27.93 ± 2.01	27.99 ± 3.27	0.929	27.96 ± 2.87	–	–
$HBeAg^+$, %	74.07	84.38	0.327	79.66	80.00	0.968
Infants, *n*	29	32	–	61[a]	34[b]	–
Gestational age, weeks	38.37 ± 1.64	38.91 ± 1.20	0.166	38.66 ± 1.43	38.94 ± 1.22	0.350
Infant weight, kg	3.30 ± 0.51	3.38 ± 0.39	0.483	3.34 ± 0.45	3.26 ± 0.40	0.745
Infant length, cm	49.67 ± 1.21	50.19 ± 0.69	0.113	49.93 ± 1.00	49.88 ± 1.02	0.805
Apgar score (1 min)	9.68 ± 1.31	9.84 ± 0.72	0.740	9.77 ± 1.03	9.88 ± 0.67	0.542
Cesarean rate, %	62.07	34.38	0.034	47.54	32.35	0.151

n number, *LAM* lamivudine, *LdT* telbivudine, *ALT* alanine transaminase, *CK* creatine kinase, *p* serum phosphorus

[a]Two pairs of twins were included in the treatment group

[b]One pair of twins were included in the control group. Two mothers in the control group experienced induced labor

Table 2 Complications and adverse events in mothers

N (%)	LAM, $n = 27$	LdT, $n = 32$	All treated, $n = 59$	Control, $n = 35$	*p* (all treated versus control)
Gestational hypertension	1 (3.7)	0 (0)	1 (1.7)	1 (2.9)	1.000
Gestational diabetes mellitus	7 (25.9)	12 (37.5)	20 (33.9)	11 (32.4)	0.806
Hyperemesis gravidarum	0 (0)	1 (3.1)	1 (1.7)	0 (0)	1.000
Membrane prerupture	5 (18.5)	7 (21.9)	12 (20.3)	8 (22.9)	0.773
Postpartum hemorrhage	3 (11.1)	2 (6.2)	5 (8.5)	1 (2.9)	0.522
Threatened abortion	0 (0)	1 (3.1)	1 (1.7)	0 (0)	1.000
Oligohydramnios	1 (5.6)	0 (0)	1 (1.7)	0 (0)	1.000
Polyhydramnios	1 (5.6)	0 (0)	1 (1.7)	0 (0)	1.000
Induced labor	0 (0)	0 (0)	0 (0)	2 (5.7)	0.136
Arrhythmia	1 (3.7)	0 (0)	1 (1.7)	1 (2.9)	1.000
CK elevation	2 (7.4)	7 (21.9)	9 (15.3)	0 (0)	0.037[*]
Hepatitis flare	0 (0)	0 (0)	0 (0)	6 (17.1)	0.004[#]

LAM lamivudine, *LdT* telbivudine, *N* number, *CK* creatine kinase

[*]$p = 0.037$ more mothers in the treated group experienced CK elevation compared with those in the control group during pregnancy

[#]$p = 0.004$ more mothers in the control group experienced hepatitis flare (ALT > 2 × baseline) compared with those in the treated group during pregnancy

lower in treated than untreated mothers (0/61 or 0 versus 4/34 or 11.76 %, $p = 0.028$). Furthermore, the effective immune response rate (anti-HBsAg ≥100 mIU/ml) was similar between the above two groups (57/61 or 93.4 versus 27/34 or 79.41 %, $p = 0.086$) (Table 5).

Table 3 HBV DNA and ALT levels at delivery for mothers with active CHB with or without treatment

Mothers, *n* (%)	LAM, $n = 27$	LdT, $n = 32$	All treated, $n = 59$	Control, $n = 33$	χ^2	*p* (all treated versus control)
HBV DNA <500 copies/ml	20 (74.07)	27 (83.38)	47 (79.66)	2 (6.06)	46.05	<0.001
HBV DNA $<10^6$ copies/ml	27 (100)	32 (100)	59 (100)	14 (42.42)	42.81	<0.001
ALT normalization	27 (100)	32 (100)	59 (100)	26 (78.79)	10.70	0.001

LAM lamivudine, *LdT* telbivudine, *n* number

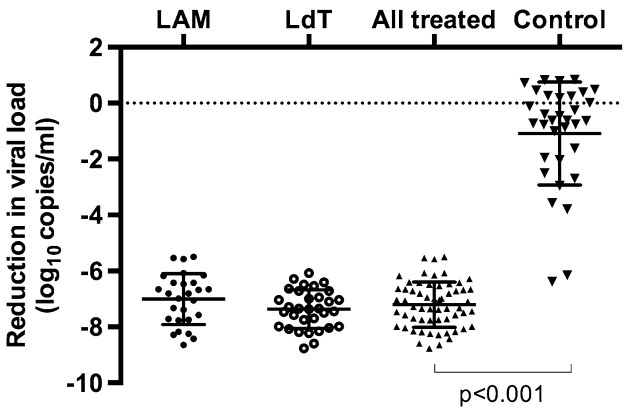

Fig. 2 Virological efficacy of antepartum lamivudine or telbivudine. Mean reduction in viral load (baseline to birth). LAM: $n = 27$; LdT: $n = 32$; control: $n = 33$. Results are mean ± SD

Discussion

To the best of the authors' knowledge, this is the first study with relatively large sample size to evaluate two kinds of NA (LAM and LdT) initiated in early pregnancy for mothers with active CHB. Our study found that NA (LAM and LdT) initiation in early pregnancy was safe for mothers with active CHB. In addition, this study demonstrated that treatment with LAM or LdT started in early pregnancy could effectively control maternal liver disease and further reduce the MTCT rate.

The safety of antiviral therapy during pregnancy is always a priority issue. However, few data exist to support the safety profile of NAs initiated in early pregnancy. Recently, a cohort study conducted by Tan et al. enrolled 169 mothers who initiated LdT in either early or late

Table 4 Adverse events in infants

N (%)	LAM, $n = 29$	LdT, $n = 32$	All treated, $n = 61$	Control, $n = 34$	*p* (all treated versus control)
Asphyxia	1 (3.4)	0 (0)	1 (1.6)	0 (0)	1.000
PTL	7 (24.1)	1 (3.1)	8 (13.1)	1 (2.9)	0.208
HDN	1 (3.4)	0 (0)	1 (1.6)	0 (0)	1.000
Neonatal jaundice	1 (3.4)	1 (3.1)	2 (3.3)	0 (0)	0.535
Macrosomia	1 (3.4)	1 (3.1)	2 (3.3)	0 (0)	0.535
LBW	3 (10.3)	1 (3.1)	4 (6.6)	1 (2.9)	0.781

N number, *PTL* preterm labor, *HDN* hemolysis disease of newborn, *LBW* low birth weight

Table 5 Virological features of infants from mothers with active CHB with or without treatment

Infants, *n* (%)	LAM, $n = 29$		LdT, $n = 32$		All treated, $n = 61$		Control, $n = 34$	
	At birth	At 28 weeks	At birth	At 28 weeks	At birth	At 28 weeks	At birth	At 28 weeks
HBsAg positive	2 (6.9)	0 (0)	2 (6.3)	0 (0)	4 (6.6)	0 (0)	16 (47.1)	4 (11.8)
HBeAg positive	7 (24.1)	0 (0)	11 (34.4)	0 (0)	18 (29.5)	0 (0)	25 (73.5)	4 (11.8)
HBV DNA detectable	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (11.8)	4 (11.8)*
Immune response[a]	–	27 (93.1)	–	30 (93.8)	–	57 (93.4)	–	27 (79.4)

LAM lamivudine, *LdT* telbivudine, *n* number

*$p = 0.028$ between treated and control group at postpartum week 28

[a]Defined as anti-HBsAg ≥100 mIU/ml at 7 months of age

pregnancy. They found no differences in maternal or infant outcomes between the early and late groups [18]. However, in that study, the sample size of mothers with active CHB in the early treatment group was relatively small ($n = 14$), and no significant differences in MTCT rate were found between the early and control group. Sun et al. also reported the clinical outcomes of mothers initiating LdT in either early or middle pregnancy [19]. Although the trial included main AEs occurring during the study period, the study failed to monitor important laboratory results, such as serum phosphorus, creatine kinase, and creatinine. In addition, one observational study from Beijing supported the safety of LAM after evaluating mothers treated with LAM either before or in early pregnancy [20]. However, that study lacked a control group. We believe that our data can make up for the deficiencies mentioned above. Our study enrolled 94 mothers with active CHB in early pregnancy. Maternal outcomes were similar between the treated and control group, except for a higher proportion of mild (grade I) CK elevation in treated mothers. Overall, 61 infants were enrolled in our study, and no significant safety concerns among them were identified during 7 months of follow-up. The above results suggest that early initiation of LAM or LdT during pregnancy for mothers with active CHB seems to be safe.

There is still no consensus regarding the optimal time to initiate antiviral therapy during pregnancy to suppress HBV DNA below a level associated with immunoprophylaxis failure. Commencing antiviral therapy in the second/third trimester could definitely reduce but may not eliminate the risk of MTCT, because the treatment duration may be too short to fully suppress HBV DNA during pregnancy. Mothers initiating NAs in the second/third trimester of pregnancy but failing to achieve HBV DNA partial control ($<10^6$ copies/ml) have been reported [10, 11, 13, 15]; when maternal HBV DNA at delivery is below this threshold, MTCT is much less likely to occur [21]. Even when achieving HBV DNA partial control, the risk of MTCT may still exist, as a recent study found that vertical transmission could still occur in mothers with low viral load ($10^3 \sim 10^6$ copies/ml) [22].

In the current study, even though the main purpose of early initiation of NA therapy was to control maternal liver disease, it was also demonstrated that this approach could thereby further reduce the risk of MTCT. We enrolled mothers with active CHB and high HBV DNA levels in early pregnancy, and 100 % of treated mothers achieved HBV DNA level $<10^6$ copies/ml at delivery. Unsurprisingly, the MTCT rate was significantly lower in treated mothers, with no vertical transmission occurring in either the LAM or LdT group. Furthermore, no viral breakthrough occurred during the pregnancy period. Therefore, our results indicate that LAM or LdT initiated in early pregnancy for mothers with active CHB is effective for reducing maternal viral load, thereby interrupting MTCT.

Some limitations of the present study should be considered. Firstly, this was a single-center, retrospective study. Secondly, TDF was not included in our study, since it was not officially approved for HBV treatment in Mainland China during the study period. In addition, safety data for LAM/LdT used in early pregnancy might not be generalizable to use during the entire pregnancy, since we only enrolled mothers initiating LAM/LdT in early pregnancy but not before pregnancy. Therefore, future multicenter prospective studies with larger sample size and longer follow-up period are still needed to further prove the safety and efficacy of NAs, especially TDF, either initiated in early pregnancy for mothers with active CHB or used during the entire pregnancy for mothers with accident pregnancy while on NA treatment.

In conclusion, initiating LAM or LdT for active CHB in early pregnancy seems to be safe for both mothers and infants, and LAM/LdT is effective for controlling maternal disease as well as interrupting MTCT. Mild CK elevation is common during such treatment and should be monitored.

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Authors' contributions Drs. He TY, Ou XJ, Cai HD, and Jia JD contributed fully to the study conception and design. Drs. Yi W, Liu M, and Cai HD contributed fully to the data collection and project supervision. Drs. He TY, Bai YQ, and Jia JD contributed fully to the manuscript writing.

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Compliance with ethical standards

Conflict of interest Jidong Jia received lecture fee and consultation fee from BMS, MSD, and Novartis pharmaceutical companies in the last 2 years. Tianyu He, Yuqing Bai, Haodong Cai, Xiaojuan Ou, Min Liu, and Wei Yi declare that they have no conflicts of interest.

Ethics approval The study protocol was approved by the medical ethics committee of Beijing Ditan Hospital, and informed consent was waived (no. BJDTEC-37). The current study complied with the Helsinki Declaration.

References

1. WHO. Global hepatitis report (internet). 2017. Available from http://apps.who.int/iris/bitstream/10665/255016/1/9789241565455-eng.pdf. Accessed July 2017

2. He T, Jia J. Chronic HBV: which pregnant women should be treated? Liver Int 2016;36(Suppl 1):105–108
3. Liang X, Bi S, Yang W, et al. Epidemiological serosurvey of hepatitis B in China-declining HBV prevalence due to hepatitis B vaccination. Vaccine 2009;27:6550–6557
4. Xin X, Wang Y, Cheng J, et al. Seroepidemiological survey of hepatitis B virus infection among 764,460 women of childbearing age in rural China: a cross-sectional study. J Clin Virol 2016;81:47–52
5. Sarin SK, Kumar M, Shrivastava S, et al. Influence of chronic HBV infection on pregnancy: a human model of maternofetal virus host interactions. Gastroenterology 2011;141(4):1522–1525
6. Lin X, Guo Y, Zhou A, et al. Immunoprophylaxis failure against vertical transmission of hepatitis B virus in the Chinese population: a hospital-based study and a meta-analysis. Pediatr Infect Dis J 2014;33(9):897–903
7. Pande C, Sarin SK, Patra S, et al. Hepatitis B vaccination with or without hepatitis B immunoglobulin at birth to babies born of HBsAg-positive mothers prevents overt HBV transmission but may not prevent occult HBV infection in babies: a randomized controlled trial. J Viral Hepat 2013;20(11):801–810
8. Brown RS Jr, McMahon BJ, Lok AS, et al. Antiviral therapy in chronic hepatitis B viral infection during pregnancy: a systematic review and meta-analysis. Hepatology 2016;63:319–333
9. Terrault NA, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016;63:261–283
10. Xu WM, Cui YT, Wang L, et al. Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multicentre, randomized, double-blind, placebo-controlled study. J Viral Hepat 2009;16:94–103
11. Pan CQ, Yi W, Liu M, et al. Lamivudine therapy during the second vs the third trimester for preventing transmission of chronic hepatitis B. J Viral Hepat 2017;24:246–252
12. Pan CQ, Han GR, Jiang HX, et al. Telbivudine prevents vertical transmission from HBeAg-positive women with chronic hepatitis B. Clin Gastroenterol Hepatol 2012;10(5):20–26
13. Han GR, Cao MK, Zhao W, et al. A prospective and open label study for the efficacy and safety of telbivudine in pregnancy for the prevention of perinatal transmission of hepatitis B virus infection. J Hepatol 2011;55:1215–221
14. Wu Q, Huang H, Sun X, et al. Telbivudine prevents vertical transmission of hepatitis B virus from women with high viral loads: a prospective long-term study. Clin Gastroenterol Hepatol 2015;13:1170–1176
15. Pan CQ, Duan Z, Dai E, et al. Tenofovir to prevent hepatitis B transmission in mothers with high viral load. N Engl J Med 2016;374:2324–2334
16. Toy M, Veldhuijzen IK, de Man RA, Richardus JH, Schalm SW. Potential impact of long-term nucleoside therapy on the mortality and morbidity of active chronic hepatitis B. Hepatology 2009;50:743–751
17. FDA. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. 2007. Available from http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceCompliance/RegulatoryInformation/Guidances/Vaccines/ucm091977.pdf. Accessed July 2017
18. Tan Z, Yin Y, Zhou J, Wu L, Xu C, Hou H. Telbivudine treatment of hepatitis B virus-infected pregnant women at different gestational stages for the prevention of mother-to-child transmission. Medicine 2016;95:e4847
19. Sun W, Zhao S, Ma L, et al. Telbivudine treatment started in early and middle pregnancy completely blocks HBV vertical transmission. BMC Gastroenterol 2017;17:51
20. Yi W, Liu M, Cai HD. Safety of lamivudine treatment for chronic hepatitis B in early pregnancy. World J Gastroenterol 2012;18(45):6645–6650
21. Zou H, Chen Y, Duan Z, Zhang H, Pan C. Virologic factors associated with failure to passive–active immunoprophylaxis in infants born to HBsAg-positive mothers. J Viral Hepat 2012;19:e18–e25
22. Chen ZX, Gu GF, Bian ZL, et al. Clinical course and perinatal transmission of chronic hepatitis B during pregnancy: a real-world prospective cohort study. J Infect 2017;75(2):146–154