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Comparison of the efficacy and safety of tenofovir and telbivudine in interrupting mother-to-child transmission of hepatitis B virus

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Abstract

The present study is aimed to evaluate and compare the efficacy and safety of tenofovir (TDF) and telbivudine (TBV) in interrupting hepatitis B virus (HBV) mother-to-child transmission (MTCT), and to provide evidence-based treatment options to clinicians and patients.

Hepatitis B e-antigen (HBeAg)-positive pregnant women (644 in total) with high HBV DNA load ($\geq 2 \times 10^5$ IU/mL) and who received TDF (n = 214) or TBV (n = 380) in the second or third trimester, or received no treatment (n = 50) were included in this retrospective analysis.

HBV DNA levels in mothers at delivery were significantly lower than baseline in the 2 treatment groups. HBV DNA levels in the TDF group were significantly different between the mothers receiving treatment in the second trimester and those receiving treatment in the third trimester; however, significant difference was not observed in the TBV group. The proportion of hepatitis B surface antigen (HBsAg)-positive infants at the age of 7 to 12 months in the TDF, TBV, and control groups were 0.00% (0/174), 0.30% (1/331), and 5.0% (2/40) with a significant difference between the treatment groups and the control group, but no difference between the TDF and TBV group ($P > .05$). However, no serious adverse events were observed in infants and mothers of all groups.

TBV and TDF can effectively reduce the HBV DNA level and MTCT rate in pregnant women with high HBV DNA load ($\geq 2 \times 10^5$ IU/mL); both antiviral drugs are safe for infants and mothers. Since TDF was more effective in reducing HBV DNA levels during the second trimester, its use during the period is recommended to prevent HBV MTCT.

Abbreviations: ALT = alanine aminotransferase, CHB = chronic hepatitis B, HBeAg = hepatitis B e-antigen, HBIG = hepatitis B immunoglobulin, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, LAM = lamivudine, MTCT = mother-to-child transmission, TBV = telbivudine, TDF = tenofovir.

Keywords: hepatitis B virus, mother-to-child transmission, telbivudine, tenofovir

1. Introduction

The World Health Organization estimates that 257 million people suffer from chronic hepatitis B (CHB) each year, resulting in 887,000 deaths worldwide from hepatitis B annually.[1] The chronic state of hepatitis B is mostly asymptomatic, and approximately one-fourth of the people infected with CHB die from cirrhosis or liver cancer (HCC), accounting for more than half of all liver cancers.[2–4] Although the combined immunization regimen of hepatitis B vaccine and hepatitis B immunoglobulin (HBIG) prevents occurrence of most CHB, 5% to 10% failure rate is likely. Approximately 90 million people having chronic hepatitis B virus (HBV) infection have been found in China, accounting for one-third of the global infection burden, the highest among all countries in the world.[5] The 2014 serological survey in people of China showed that the hepatitis B surface antigen (HBsAg) is high (8.3%) among people aged between 20 to 29 years, and with its annual birth cohort size of 16.97 million, 750,000 to 1 million infants are born to HBsAg-positive mothers.[6,7] Globally, countries with high prevalence of hepatitis B also experience poor living conditions.[8] Multiple studies have shown that the important risk factors associated with immunization failure are HBsAg-positive mothers with CHB and/or high load of HBV; moreover, high viral load is considered to be an independent risk factor.[9–11] HBV consists of 2 parts: outer shell and core. HBsAg is located on the surface of the virus, whereas hepatitis B core antigen and hepatitis B

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e-antigen (HBeAg) are present inside the core. HBsAg is the first serological indicator to appear and can be used in the early diagnosis of hepatitis B. HBeAg and HBV DNA are closely related, and reflect the activity of viral DNA replication. HBeAg positive indicates the active phase of HBV infection. HBV DNA level $\geq 10^6$ copies/mL in mother was associated with significant increase in failure rate of mother-to-child transmission (MTCT) interruption, with infection rate of 2.5%. At mother's serum HBV DNA level of 10^8 copies/mL, the infection rate reached 12.4%.[12,13] After the approval of Global Health Sector Strategy on Viral Hepatitis 2016 to 2021 by the World Health Assembly, the World Health Organization produced a strategy to eliminate HBV by 2030. One of the 5 aims to achieve the goal of eliminating HBV is to prevent HBV MTCT.

In order to achieve MTCT interruption of hepatitis B, nucleotide analogues have been recommended to treat pregnant women with high viral load during pregnancy.[14–16] Studies have shown that lamivudine(LAM) has a significant effect in reducing the risk of MTCT, but the problem of drug resistance induced by viral mutations caused by its long-term use is worthy of attention.[17] In previous studies, tenofovir (TDF) and telbivudine (TBV) have been reported as more effective than LAM in interrupting HBV MTCT and against development of drug resistance.[18] Toxicological studies have shown that TBV has no carcinogenicity, teratogenicity, or mutagenicity.[19] TDF is approved for the treatment of hepatitis B recently; it shows excellent efficacy and demonstrates the highest barrier to drug resistance.[20,21] Several studies have been conducted on determining the effectiveness of TDF or TBV to interrupt HBV MTCT, and demonstrated their efficacy and safety.[22,23] However, there are few studies on effectiveness of TDF to prevent MTCT in HBeAg-positive pregnant women with CHB and high viral load, particularly the comparison of efficacy and safety between TDF and TBV. This makes clinicians and pregnant women lack the necessary evidence to choose between these drugs. Therefore, we conducted the present study aimed to compare the efficacy and safety of TDF and TBV, and provide evidence for future clinical treatment.

1.1. Study design

We selected HBsAg-positive pregnant women who sought advice from physicians at the Fifth Hospital of Shijiazhuang and Shijiazhuang Maternal and Child Health Hospital between January 2017 to May 2019. The inclusion criteria for women participated in the study were:

1. 20 to 40 years old;
2. 20 to 32 weeks of gestation;
3. positive for serum HBsAg and HBeAg for a period of at least 6 months;
4. with HBV DNA load $\geq 2 \times 10^5$ IU/mL;
5. had alanine aminotransferase (ALT) below 10 times the upper limits of normal (ULN: 40 IU/mL);
6. took a standard pregnancy test before 22 to 24 weeks of pregnancy and had at least 2 obstetric ultrasound examination results; and
7. all infants received passive-active immunoprophylaxis with HBIG and vaccine within 12 hours of birth, followed by additional vaccine doses at 1 and 6 months of age.

Pregnant women were excluded based on the following criteria:

1. occurrence of CHB in husband;
2. had other viral infections, including hepatitis A virus, hepatitis C virus, hepatitis D virus, human immuno-deficiency virus, and Epstein-Barr virus,
3. received previous treatment with interferon or nucleoside analogues;
4. diagnosed with cirrhosis, liver cancer, and liver failure;
5. showed clinical signs of threatened abortion; and
6. examination found evidence of fetal malformation.

The women included in the study received daily treatment with TBV/TDF/no drug in the control group until the end of the pregnancy. Pregnant women who used other drugs for antiviral treatment were not included in the study. They were grouped as the TDF group (patients receiving TDF 300 mg per day), the TBV group (patients receiving TBV 600 mg per day), and the control group (patients not receiving any antiviral treatment). The Ethics Review Committee of the 2 hospitals approved the study and waived the requirement to obtain informed consent.

We conducted a retrospective review of hospital obstetric data using the electronic medical record and inspection systems, and screened the cases according to our inclusion and exclusion criteria. We collated the following retrospective data:

1. maternal basic demographic data: ethnicity, telephone numbers, time of consultation, gestational week, previous pregnancy, illness and medication history, family history of hepatitis B, symptoms or discomfort;
2. maternal baseline condition: serum HBV markers and HBV DNA level, liver biochemical indicators, time and dosage of antiviral therapy;
3. maternal condition at delivery: serum HBV markers and HBV DNA level, liver biochemical indicators, symptoms or discomfort, delivery methods, postpartum hemorrhage;
4. neonatal data: gestational age, gender, Apgar score, body weight, amniotic fluid volume and dyeing degree, injury and deformity, the proportion of intrauterine distress, serum HBV markers and HBV DNA level; and
5. serum HBV markers and HBV DNA level in infants during 7 to 12 months of their age.

2. Methods

Quantitative fluorescence polymerase chain reaction (QF-PCR, Daan Gene Co., Ltd.) was used to determine serum HBV DNA level; serum HBV markers were determined by chemiluminescence technology (Abbott Diagnostics). Liver functions were detected using a fully automated biochemistry analyzer. These markers were measured during patient visit, including at the beginning of the study before the start of the treatment, at delivery, and at the time of any discomfort throughout the entire pregnancy and after delivery, also including at the time of birth and 7 to 12 months after birth.

2.1. Assessment

2.1.1. Efficacy. The primary efficacy endpoint was the rate of perinatal HBV transmission (HBsAg-positive or HBV DNA-positive detection in infants at the age of 7–12 months). Secondary efficacy endpoints included reduction in maternal serum HBV DNA level, and the rates of HBeAg clearance and HBeAg seroconversion in mothers at delivery.

2.1.2. Safety. Incidence rate of deformities and injuries, Apgar score, weight, caesarean section rate, and proportion of babies with low birth weight and premature delivery were assessed for all infants. The symptoms and discomfort in mothers from baseline to delivery were recorded. Additionally, ALT and creatine kinase levels in mothers were measured.

2.2. Statistical analysis

Continuous variables are presented as mean ± SD, and analyzed by one-way ANOVA or Student *t* test. Categorical variables were compared by Chi-Squared test or Fisher exact test. *P* value less than .05 was considered statistically significant. All *P* values and confidence intervals were based on a two-tailed test. All data were analyzed by the SPSS software (version 23.0,).

3. Results

3.1. Baseline characteristics of enrolled patients

The study included a total of 644 pregnant women who met the inclusion criteria, including 594 women who received antiviral therapy (214 in the TDF group and 380 in the TBV group), and 50 in the control group who did not receive any antiviral treatment, as shown in the process flowchart (Fig. 1). There was no statistical difference in the average age of pregnant women in the 3 groups: TDF group 27 ± 3.99 (range: 20–39), TBV group 28.04 ± 3.71 (range: 20–38), and control group 27.88 ± 3.20 (range: 23–35). In the TDF group, pregnant women received 300 mg of TDF daily orally; the group included 125 women in the second trimester and 89 in the third trimester of their pregnancy. In the TBV group, 257 and 123 pregnant women were in the second and third trimester, respectively; all women in the group received 600 mg of TBV daily orally. Their baseline HBeAg level, HBV DNA level, and ALT level were not significantly different (Table 1). A total of 41 pregnant women had elevated ALT (ALT > 40 IU/mL) at baseline, including 9.8% (21/214) of the TDF group, 5.0% (19/380) of the TBV group, and 2.0% (1/50) of the control group ($P = .025$).

3.2. Effectiveness of drugs in mothers

All mothers who received antiviral therapy showed a significant decrease in HBV DNA level at delivery compared with baseline ($P < .05$), with an average decrease of 2 $\log_{10}$IU/mL. Pregnant women in the TDF group and TBV group began to receive antiviral therapy at the gestational week of 27.57 ± 3.99 and 28.04 ± 3.71, respectively. Baseline HBV DNA levels in the TDF

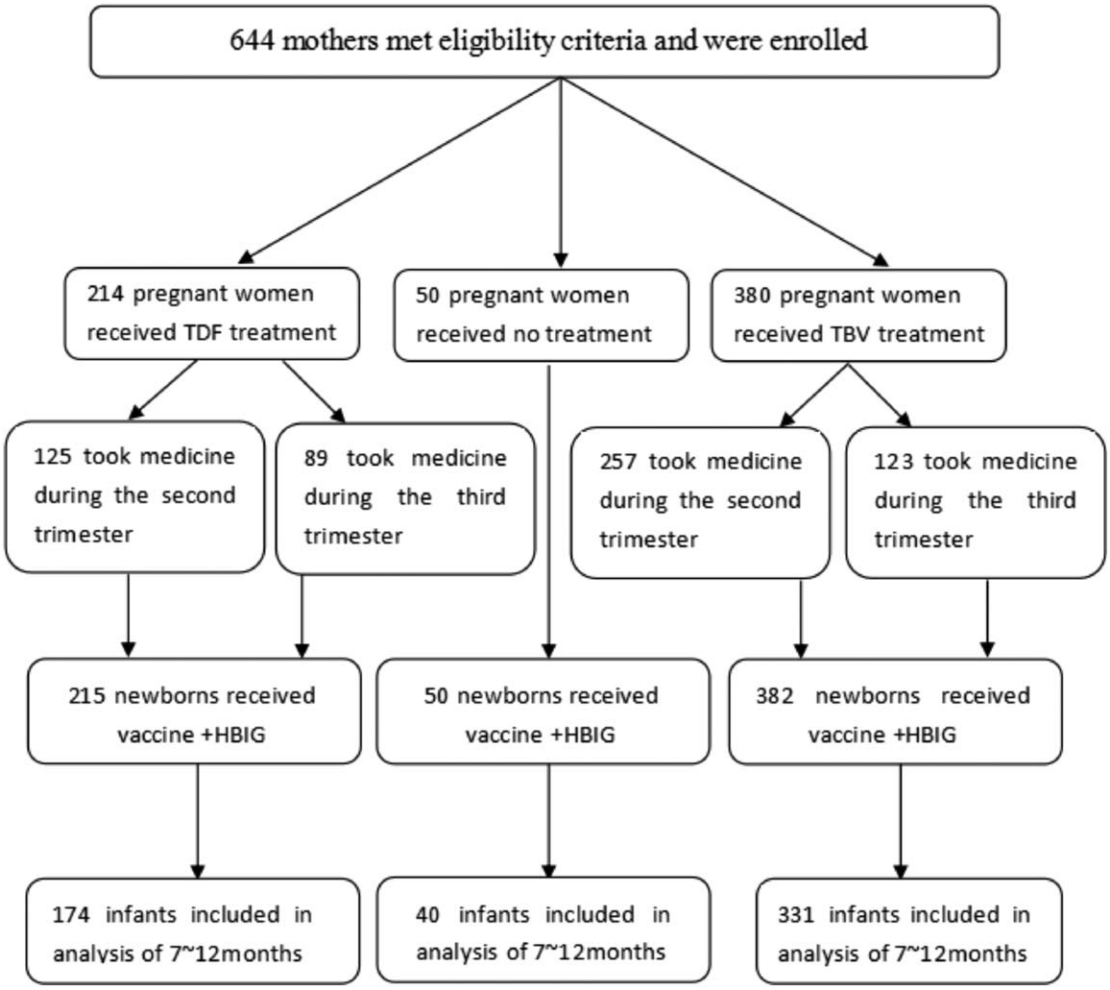

Figure 1. Disposition of mothers and infants.

Table 1

Baseline characteristics of mothers.

	TDF treated (214)	TBV treated (380)	Nontreated (50)	F/ χ^2	*P*
Age, years (mean ± SD)	27.57 ± 3.99	28.04 ± 3.71	27.88 ± 3.2	1.106	.331
Previous pregnancy (mean ± SD)	2.05 ± 0.95	2.18 ± 1.00	2.32 ± 1.15	2.071	.127
HBeAg titer, S/CO	1385.34 ± 362.65	1553.92 ± 2387.98	1537.47 ± 190.02	0.582	.559
ALT level, U/L	23.51 ± 16.23	20.24 ± 26.80	31.48 ± 85.49	1.941	.148
Elevated ALT, n (%)*	21 (9.80)	19 (5.00)	1 (2.00)	5.050	.025
HBV DNA level (log_{10} IU/ mL)†	8.19 ± 8.58	8.11 ± 8.71	7.78 ± 7.78	0.911	.403
≥8log_{10}IU/mL, n (%)	98 (45.80)	216 (56.80)	11 (22.00)	6.706	.010
≥7log_{10} IU/mL, n (%)	89 (41.60)	134 (35.30)	33 (66.00)	17.882	<.001
≥6log_{10} IU/mL, n (%)	24 (11.20)	22 (5.80)	4 (8.00)	5.632	.060
≥5log_{10} IU/mL, n (%)	3 (1.40)	8 (2.10)	2 (4.00)	1.741	.391

* Elevated ALT was defined when the value of ALT level is higher than 40 U/L.

† The lower limit of detectable HBV DNA was 200 IU per milliliter.

§ALT = alanine aminotransferase, CK = creatine kinase, HBeAg = hepatitis B e antigen, HBsAg = hepatitis B surface antigen, TBV = telbivudine, TDF = tenofovir.

Table 2

The characteristics of mothers at delivery.

	TDF treated (214)	TBV treated (380)	Nontreated (50)	F/X^2	*P*
ALT level, U/L (mean ± SD)	19.05 ± 25.14	15.86 ± 11.95	13.01 ± 5.54	3.40	.034
Elevated ALT n (%)*	11 (5.14)	4 (1.05)	0 (0.00)	9.293	.002
HBeAg clearance, n (%)	7 (3.30)	2 (0.53)	–	5.195	.023
HBeAg seroconversion, n (%)	6 (2.80)	2 (0.53)	–	3.768	.052
Elevated CK, n (%)	21 (9.81)	25 (6.58)	1 (2.00)	4.977	.083
Gastrointestinal symptoms,n (%)	7 (3.27)	21 (5.53)	5 (10.00)	4.083	.116
HBV DNA level (log_{10} IU/ mL)	6.23 ± 7.24	6.13 ± 7.11	7.74 ± 8.05	5.695	.004
≥5 log_{10} IU /mL, n (%),	37 (17.29)	34 (8.95)	32 (64.00)	100.074	<.001
<5 log_{10} IU /mL, n (%)	177 (82.71)	346 (91.05)	18 (36.00)	100.074	<0.001

* Elevated ALT was defined when the value of ALT level is higher than 40 U/L.

group and TBV group were 8.19 ± 8.58 log_{10}IU/mL and 8.11 ± 8.71 log_{10}IU/mL, and HBV DNA level ≥8 log_{10}IU/mL was observed in 45.8% (98/214) and 56.8% (216/380) of women in the 2 groups respectively. After treatment, the HBV DNA level in the 2 groups was 6.23 ± 7.24 log_{10}IU/mL and 6.13 ± 7.11 log_{10} IU/mL, and the proportion of women having HBV DNA level ≥8 log_{10}IU/mL in the 2 treatment groups was reduced to 0.47% and 0.53%, respectively (Supplemental Digital Content, Table S1, http://links.lww.com/MD2/A628). However, the HBV DNA level at delivery remained unchanged from baseline (7.78 ± 7.78 log_{10}IU/mL at baseline vs 7.74 ± 8.05 log_{10}IU/mL at delivery, $P > .05$) in pregnant women in the control group. Moreover, In the TDF group, a statistically significant difference in the HBV DNA level at delivery was observed between mothers who started treatment during the second and those during the third trimester ($P < .001$, Supplemental Digital Content, Table S2, http://links.lww.com/MD2/A629), but there was no significant difference in the TBV group ($P = .081$). HBeAg clearance rate was 3.30% and 0.53% in the TDF and TBV groups, respectively ($P = .023$). In addition, there was no significant difference in HBeAg seroconversion rate between the 2 drug groups (6/214 [2.80%] vs 2/380 [0.53%], $P = .052$) (Table 2).

3.3. Effectiveness of drugs in infants

Six hundred forty four pregnant women gave birth to 647 babies, with 1 set of twins in the TDF group and 2 sets of twins in the TBV group. All newborns were vaccinated with hepatitis B vaccine and HBIG within 12 hours of birth. The basic character-

Table 3

Clinical characteristics of infants.

	TDF treated (215)	TBV treated (382)	Nontreated (50)	F/X^2	*P*
Gestational age (wks)	38.74 ± 1.47	38.89 ± 1.20	39.10 ± 1.18	1.944	.144
Cesarean section, n (%)*	84 (39.25)	164 (43.16)	25 (50.00)	1.427	.490
Apgar score, (mean ± SD)	9.86 ± 1.00	9.98 ± 0.12	9.90 ± 0.40	2.480	.089
Birth weight, g	3230.62 ± 439.05	3290.82 ± 416.13	3343.06 ± 447.71	2.024	.133
Low birth weight, n (%)	7 (3.36)	10 (2.62)	1 (2.00)	0.298	.864
Premature birth, n (%)	17 (7.91)	15 (3.93)	1 (2.00)	4.907	.083
HBsAg positive in birth, n (%)	19 (8.84)	18 (4.71)	4 (8 .00)	4.401	.116
HBsAg positive at 7~12 mo, n (%)†	0 (0.00)	1 (0.30)	2 (5.00)	7.678	.015

* The total number of cases in the 3 groups are 214, 380, and 50, respectively.

† The total number of cases in the 3 groups are 174, 331, and 40, respectively.

Table 4

Information on infants who failed to interrupt MTCT.

	Case-1	Case-2	Case-3
Treatment	TBV	No	No
Age of mothers	32	34	33
Start treatment time (wks)	34	NA	NA
Baseline HBV DNA level of mothers (log_{10} IU /mL)	7.97	8.75	7.57
Baseline HBeAg level of mothers (S/CO)	1760.04	1432.42	1116.25
HBV DNA level of mothers at delivery, (log_{10} IU /mL)	7.29	8.39	7.01
Delivery method	Cesarean section	Natural delivery	Cesarean section
Birth weight (g)	3200	3100	3150
HBsAg level of newborns at delivery, (IU/mL)	2.09	1.15	4.39
HBV DNA level of newborns at delivery, (IU/mL)*	<200	<200	<200
HBsAg level of newborns at 7∼12 mo, (IU/mL)	1.85	1.07	2.03
HBV DNA level of newborns at 7∼12 mo,(IU /mL)	<200	<200	<200

* The lower limit of detectable HBV DNA was 200 IU per milliliter.

istics of newborns are shown in Table 3. The proportion of HBsAg-positive newborns in the TDF group, TBV group, and control group were 8.84% (19/215), 4.71% (18/382), and 8.00% (4/50), respectively ($P = .116$).

Due to lack of follow-up, we missed the postnatal data of 102 babies. Among infants aged 7 to 12 months, the proportion of HBsAg-positive infants in the TDF group, TBV group, and control group were 0.0% (0/174), 0.3% (1/331), and 5.0% (2/40), respectively. Both antiviral treatment groups showed significant differences in the rates of HBsAg-positive infants aged 7 to 12 months compared with the control group ($P = .015$), however, the difference was not significant between the TDF group and TBV group ($P > .99$). In addition, none of the infants were positive for HBV DNA (HBV DNA > 200 IU/mL) in the 3 groups. The characteristics of 3 infants who showed failure of MTCT interruption are shown in Table 4. It was observed that their mothers' baseline HBV DNA levels were greater than 7.5 log_{10} IU/mL and greater than 7.0 log_{10} IU/mL at delivery. HBeAg levels of these mothers were 1760.04 S/CO, 1432.42 S/CO, and 1116.25 S/CO at baseline. The mother in the TBV group whose infant had positive HBsAg at 7 to 12 months received treatment in the third trimester.

3.4. Safety of drugs in mothers

At delivery, the average ALT levels in mothers of the TDF group, TBV group, and control group were 19.05 ± 25.14 IU/mL, 15.86 ± 11.95 IU/mL, and 13.01 ± 5.54 IU/mL, respectively, which were significantly different ($P = .034$). The rate of elevated ALT in the TDF and TBV groups were 5.14% (11/214) and 1.05% (4/380) ($P = .002$). There was no significant difference in the rate of elevated CK between the 3 groups (Table 2). In the TDF group, TBV group, and control group, there were 39.25% (84/214), 43.16% (164/380), and 50% (25/50) pregnant women preferred to have a cesarean section, respectively, showing no difference in the rates of cesarean section among the 3 groups ($P > .05$). In the 3 groups, 3.27% (7/214), 5.53% (21/380), and 10% (5/50) pregnant women, respectively, developed gastrointestinal symptoms such as nausea and vomiting ($P = .116$). These indicators did not vary significantly during different pregnancy periods in the TDF and TBV groups.

3.5. Safety of drugs in infants

No abnormalities of placenta, fetal malformations, and skin and mucous membrane damage were observed in the 3 groups of infants. The average Apgar scores ($P = .089$) and birth weight ($P = .133$) of the TDF group, TBV group, and control group of newborns were not statistically different. Respectively, there were 3.36% (7/215), 2.62% (10/382), and 2% (1/50) infants with low birth weight in the TDF, TBV, and control groups with no statistical difference ($P = .864$). Furthermore, the rates of premature birth were 7.91% (17/215), 3.93% (15/382), and 2% (1/50) in the 3 groups, respectively, which were not statistically different ($P = .083$). Moreover, the rates of low birth weight and premature birth in the TDF and TBV groups did not vary significantly during different pregnancy periods ($P > .05$).

4. Discussion

The present results demonstrated that the MTCT rate of hepatitis B in the TDF group, TBV group, and control group were 0% (0/174), 0.30% (1/331), and 5.00% (2/40)(Table 3), respectively. The MTCT rates in the antiviral treatment groups were significantly lower than that in the control group, but there was no significant difference between the TDF group and TBV group ($P > .05$) regarding MTCT rates. These findings indicate that antiviral drug treatment during pregnancy can effectively interrupt the HBV MTCT, and the corresponding effects of TDF and TBV are nearly similar.

Both TBV and TDF are nucleoside analogues and HBV reverse transcriptase inhibitors. Some studies have shown that the occurrence of intrauterine infection is related to the HBV DNA level before delivery rather than at 28 weeks of pregnancy.[24] The results of study by Zou et al showed approximately 100% success rate of MTCT interruption corresponding to mothers' serum HBV DNA level at delivery $< 10^6$ copies/mL.[11] MTCT interruption failure may occur at viral DNA level $> 10^6$ copies/mL, and the failure rate increases with respect to increase in the viral load. The HBV DNA level is an independent risk factor that determines MTCT, and antiviral drugs can interrupt MTCT by inhibiting HBV DNA replication. In this study, the HBV DNA levels in most women with high viral load before treatment dropped to 2 to 4 log_{10} IU/mL at delivery in both treatment groups. However, the level of HBV DNA in the control group remained unchanged (7.78 ± 7.78 log_{10} IU/mL at baseline vs 7.74 ± 8.05 log_{10} IU/mL at delivery, $P > .05$). The proportion of mothers with HBV DNA load < 5 log_{10} IU/mL in the TDF group, TBV group, and control group were 82.71% (177/214), 91.05% (346/380), and 36.00% (18/50) ($P < .05$, Table 3), respectively. These results confirm that antiviral drug treatment during pregnancy can significantly

reduce the viral load in pregnant women, thereby playing an important role in improving the HBV MTCT interruption.

Different guidelines recommend different timings of starting antiviral therapy during pregnancy. Guideline of Prevention and Treatment for Chronic Hepatitis B of China recommends that pregnant women with HBV DNA load $> 2 \times 10^5$ IU/mL in the second or third trimester of pregnancy can receive initial antiviral treatment of TDF or TBV between 24 to 28 weeks of pregnancy.[25] The European Association for Liver Research also recommends start of the treatment during 24 to 28 week of pregnancy.[26] The American Association for the Study of Liver Diseases[15] and the Asia-Pacific Association for the Study of Liver Diseases recommend initiation of maternal antiviral treatment should be between 28 to 32 weeks of pregnancy. Similarly, different studies suggested different timings of initiation of antiviral therapy. A study by Liu et al compared the outcomes in 32 pregnant women taking TBV in early pregnancy with 50 pregnant women who were treated in late pregnancy.[27] The early pregnancy medication group resulted in 2 cases of MTCT($P < .05$). The study results were suggestive of taking antiviral drugs from the second trimester to prevent MTCT.[26] Study by Lin et al demonstrated that HBsAg/HBeAg positive mothers who start taking antiviral drugs at 24 weeks of gestation can effectively prevent HBV MTCT without adverse events.[28] However, the study by Yi et al, which included patients who started MTCT interruption in late pregnancy and those who started taking antiviral drugs before pregnancy, showed that the time to start treatment has no relationship with its efficacy.[24] Our study included pregnant women who started taking antiviral drugs either during the second or the third trimester. The results showed that the HBV DNA level in pregnant women who received TDF during the second trimester was significantly lower than that during the third trimester (3.57 ± 0.86 vs 4.40 ± 1.32 $\log_{10}$ IU/mL, $P < .001$), and the proportion of women with HBV DNA level $< 2 \times 10^5$ IU/mL at delivery was significantly higher in the former than in the latter group (93.6% [117/125] vs 66.29% [59/89], $P < .001$). However, there were no statistically significant differences in the HBV DNA level (3.88 ± 0.85 vs 3.97 ± 1.14 $\log_{10}$ IU/mL, $P = .421$) and the proportion of women with HBV DNA level $< 2 \times 10^5$ IU/mL (93.00% [239/257] vs 87.00% [107/123], $P = .082$) between the pregnant women who took TBV during the second trimester and during the third trimester. Moreover, regardless of whether TDF was taken during the second or third trimester, there was no failure of MTCT interruption. However, 1 case indicating failure of MTCT interruption was observed in the TBV group; the woman started taking antiviral drug during the third trimester. In addition, the HBV DNA level in the woman at delivery was 7.29 $\log_{10}$ IU/mL, which was higher than 2×10^5 IU/mL. Therefore, it is speculated that antiviral treatment during the second trimester may more effectively reduce the HBV DNA levels in pregnant women and increase the success rate of MTCT interruption.

In our study, all pregnant women were HBeAg positive. Multiple studies have shown that the existing immunization regimen of HBIG and hepatitis B vaccine can help completely protect the children born to HBeAg-negative pregnant women with CHB against hepatitis B.[20,24,29] The baseline HBeAg level in the TDF group, TBV group, and control group were 1385.34 ± 362.65, 1553.92 ± 2387.98, and 1537.47 ± 190.02 S/CO, respectively. We observed that antiviral drug treatment increased the conversion rate of HBeAg at delivery, and this effect was more pronounced in the TDF group than in the TBV group (7 [3.3%] vs 2 [0.53%], $P < .05$). Previous studies have shown that high HBeAg levels are associated with high HBV DNA loads. Therefore, the occurrence of maternal HBeAg seroconversion might be another reason for decrease in the HBV DNA level. In the TDF, TBV, and control groups, respective 3.27% (7/214), 5.53% (21/380), and 10.00% (5/50) pregnant women developed gastrointestinal symptoms such as nausea and vomiting ($P = .116$). Therefore, the effect of antiviral drugs on increase in gastrointestinal discomfort is precluded.

Among all participants, we observed 15 women with abnormal ALT levels at delivery, including 5 women with baseline ALT levels higher than normal and 10 with elevated ALT levels after antiviral treatment. The proportion of pregnant women with elevated ALT levels was 5.44% (11/202) and 1.11% (4/361) in the TDF group and TBV group, respectively. TDF treatment more likely caused increase in ALT level in pregnant women ($P < .05$). Several other studies also revealed increased ALT levels in mothers taking antiviral drugs. A study on TBV and LAM showed that the incidence of severe hepatitis episodes (ALT $> 10 \times$ ULN) was 17.1% among treated mothers, which was higher than that in untreated mothers (6.3%).[30] Another study on a mixed population of mothers receiving either LAM or TDF showed that the incidence of postnatal ALT elevation (>95 U/L) in the treatment and nontreatment groups was 40% to 50% and 29%, respectively.[31] Interestingly, study by Chen et al showed that pregnant women who took TDF from 30 to 32 weeks of gestation until 1 month postpartum had significantly lower ALT levels at 2 months postpartum than the control group, suggestive of possible amelioration of ALT level by TDF treatment.[32] According to study by Han et al, only 88 mothers showed considerable elevation of ALT levels after drug withdrawal that was restored to within normal range at 4 months postpartum.[33] These findings indicate that clinicians to consider the indications strictly and observe liver function indicators closely during antiviral therapy in pregnant women.

The safety of the infant is another equally important concern. In this study, antiviral treatment did not cause deformities, stillbirths, and other adverse pregnancy outcomes. In addition, premature babies (TDF: 7.91% [17/215] vs TBV: 3.93% [15/382] vs control: 2.00% [1/50], $P = .083$) and low-birth weight babies (TDF: 3.36% (7/215) vs TBV: 2.62% [10/382] vs control: 2.00% [1/50], $P = .864$) were born in all 3 groups disregarding antiviral therapy. Since antiviral therapy did not show significant increase in the proportion of babies with low birth weight and preterm birth, this indicates that antiviral therapy is safe for infants born to mothers with high levels of HBV DNA.

Nevertheless, this study is limited by its retrospective nature and lacking observation indicators. Moreover, the lack of follow-up by shedding rate of babies at 7 to 12 months after birth has affected the data integrity and accuracy to a certain extent. In addition, data related to long-term effects of drugs on babies and effects of drug withdrawal on mothers are crucial for drug selection. Additionally, effects of breastfeeding were not shown in our data. Therefore, we need additional prospective, multicenter, double-blind studies for long-term observations and to obtain more reliable and robust data.

Collectively, TDF or TBV treatment during pregnancy can effectively reduce HBV DNA levels at delivery in pregnant women who had high HBV DNA load, thereby significantly increase the success rate of HBV MTCT interruption without serious adverse events in mothers and infants. The study demonstrated significantly similar efficacy and safety of antiviral

treatment with TDF and TBV in MTCT interruption. TDF treatment during the second trimester reduced HBV DNA load more significantly than during the third trimester, while there was no significant difference in the incidence of adverse reactions. Considering the present findings, we recommend that pregnant women with high HBV DNA load start taking TDF in the second trimester to interrupt HBV MTCT.

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