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How long after giving birth should a woman with a high HBV load stop taking tenofovir to prevent the spread of the virus to her unborn child?

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Abstract

The goal of this research is to determine how long it takes for pregnant women with high hepatitis B virus (HBV) loads to stop taking tenofovir disoproxil fumarate (TDF) after giving birth in order to prevent the infection from reaching their unborn children. A total of seventy-seven pregnant women with high HBV densities who were seen at the Southern Central Hospital in Yunan Province between February 2020 and February 2021 had their clinical data retrospectively analyzed. They were divided into three groups according to when they stopped taking their drugs: group A (24 participants), group B (26 participants), and group C (27 participants)—all based on the time following delivery. Prior to birth, all three groups were administered TDF. The Roche detection system was used to evaluate liver function using alanine aminotransferase (ALT). The fluorescent quantitative approach was used to assess hepatitis B virus deoxyribonucleic acid (HBV-DNA). We used a chemiluminescence microparticle immunoassay (CMIA) to assess hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg). After 2, 4, 8, 12, 18, and 24 weeks of drug abstinence, all tests were conducted. After 2, 4, 8, 12, 18, and 24 weeks of medication discontinuation, all metrics in all three patient groups reverted to normal values. One month after delivery, 83 newborns tested negative for hepatitis B surface antigen and DNA, indicating a complete cessation of transmission from mothers to their infants and the absence of HBV infection. There was no statistically significant difference between groups A, B, and C in terms of the occurrence of adverse responses in pregnant women; the rates were 16.67%, 19.24%, and 18.52%, respectively ($p > 0.05$). Researchers found no correlation between the amount of time it took to wean the mother off of her medicine after giving birth and the therapeutic efficacy of TDF for these women. In order to confirm the findings, future studies will need to use larger samples. Late pregnancy and high levels of hepatitis B virus (HBV) are important concepts. The drug known as tenofovir disoproxil fumarate, Prevention of human papillomavirus (HBV) transmission from mothers to their children, Length of withdrawal

INTRODUCTION

There is a high incidence of HBV infection in China. According to epidemiological investigations [1,2], the domestic HBV carrier rate is about 7 – 8 %. The virus is transmitted mainly through the blood, mother-to-child, close contact, and iatrogenic routes, amongst which parturient-fetal transmission is a major method. Therefore, one of the issues of contemporary discourse in medicine is how to effectively block fetal contact with HBV through the mother [3-5]. In recent years, with the advent of hepatitis B vaccine, the prevention

of HBV and treatment of the virus carriers in hospitals with vaccination in combination with immunoglobulin, have greatly reduced the risk of HBV infection. However, vaccination is ineffective in 5 – 10 % of the population. The HBV-DNA is the most direct, sensitive and specific indicator of HBV virus infection. Positive HBV-DNA indicates that HBV is replicative and infectious [6].

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Early medical studies found that in pregnant HBV patients, lamivudine reduces HBV infection rate in newborns [7]. However, clinical studies have shown that the drug has many side effects, including general malaise, headache, fatigue, diarrhea, even allergy and other adverse reactions, and its safety cannot be guaranteed [8]. The drug TDF, a new type of nucleotide reverse transcriptase inhibitor and a class B drug for pregnancy, effectively combats a variety of viruses, and it is widely used to treat various infectious diseases [9,10].

Since the drug has been marketed only for a short time in China, there are limited clinical studies on its efficacy. Therefore, the present research was done in order to study further the withdrawal time of TDF after delivery for parturient women with high HBV density who took TDF close to delivery period so as to block fetal contact with HBV.

METHODS

Data on patients

The clinical data of 77 pregnant women near delivery period, who had high HBV density, and who came to Southern Central Hospital of Yunan Province, Mengzi, China from February 2020 to February 2021, were retrospectively analyzed. They were divided into immediate withdrawal group after delivery (n = 24), 1 month after delivery withdrawal group (n = 26), and 3 months after delivery withdrawal group (n = 27), according to the patients' personal wishes.

Inclusion criteria

Patients in the following categories were in the inclusion list: those who were confirmed with HBV infection using HBV screening test; patients aged 20 - 40 years; those who were HBsAg positive for more than 6 months, and patients with fibroscan less than or equal to 7.3 KPa.

Exclusion criteria

Parturient women with abnormal liver function; patients with other liver diseases; patients who took anti-HBV drugs before and during pregnancy; patients

who took other drugs such as immunomodulators, hormones or cytotoxic drugs, and those with threatened abortion or fetal abnormalities, were excluded in this study.

Ethical approval

This study received approval from the ethical authority of Southern Central Hospital of Yunan Province (approval no. 20210422). The study procedures were carried out following the guidelines of Declaration of Helsinki [11] and were explained to patients and their families, and duly signed consent forms were obtained from them.

Treatment protocol

At 24 - 28 weeks of gestation, the three groups of pregnant women were treated once daily with 300 mg of TDF (GlaxoSmithKline Co. Ltd.; NMPA approval No.: H20153090; specification: 300 mg). In group A, TDF was stopped immediately after delivery, while it was stopped 1 month after delivery in group B. In group C, it was stopped 3 months after delivery. The three groups of parturient women returned to hospital regularly during pregnancy and after drug withdrawal for follow-up observation. Medication was discontinued immediately if patients had serious adverse reactions during treatment. All newborns were injected with 100 IU of hepatitis B immunoglobulin within 12 h after birth. Moreover, 10 µg of hepatitis B vaccine was injected intradermally into the deltoid muscle with 24 h, and at 1 and 6 months after birth. The neonates were regularly followed up by the hospital.

Evaluation of parameters/indices

Detection of hepatitis B virus markers (HBV-M)

Following stoppage of TDF administration, chemiluminescent microparticle immunoassay kit (Abbott Laboratories) was used by the laboratory department of our hospital to determine levels of HBeAg and HBsAg indicators in the three groups of parturient women at weeks 2, 4, 8, 12, 18 and 24.

HBV-DNA



Fluorescence quantitative detection kit (Kaijie Bioengineering Co. Ltd) was used for assaying concentrations of HBV-DNA indicator in the three groups at weeks 2, 4, 8, 12, 18, and 24 following stoppages of TDF administration.

Biochemical indicator of liver function

The Roche test system was used to assay serum ALT in the three groups of patients at weeks 2, 4, 8, 12, 18, and 24 following stoppages of TDF administration. All laboratory tests were performed with the same equipment and unified reference standard.

HBV markers and HBV-DNA criteria

The diagnostic uses of various levels of HBV markers are shown in Table 1.

HBV infection in newborns

A 5-mL sample of peripheral blood was collected from each of the newborns in the 3 groups immediately after birth, 1 month after birth, and 6 months after birth. The serum markers of HBV were determined using ELISA, with positive HBV-DNA and positive HBsAg regarded as HBV infection in newborns, thereby indicating unsuccessful blocking of maternal HBV transfer to offspring.

Incidence of adverse reactions

The adverse reactions seen in all pregnant women were recorded during treatment. These included slight nausea, vomiting, dizziness and fatigue.

Statistics

This study adopted SPSS 21.0 software for data processing. Results from enumeration and measurements are presented as n (%) and mean \pm standard deviation (SD), and were compared using χ^2 test and *t*-test, respectively. Values of $p < 0.05$ were taken as indicative of statistical significance.

RESULTS

General data of the pregnant women

Table 2 shows that general data on age, gravidity, parity, number of natural births and number of cesarean sections were comparable among the three groups of pregnant women ($p > 0.05$).

Levels of HBV and liver markers in pregnant women in group A

The results shown in Table 3 indicate that the 4 markers, i.e., HBeAg, ALT, HBsAg and HBV-DNA returned to normal levels at different times after drug withdrawal in group A.

Levels of various markers after TDF withdrawal in pregnant women in group B

As shown in Table 4, the 4 indices were returned to normal levels at different times after TDF withdrawal in group B.

Table 1: HBV markers and HBV-DNA diagnosis criteria

Marker	Reference value	Unit	HBV diagnosis
HBV-DNA	<1000	cps/mL	It was positive and infectious if the value obtained was equal to or more than the reference value.
HBeAg	≤ 0.5	PEIU/mL	It was positive if the value was higher than the reference value.
HBsAg	<0.5	ng/mL	It was positive if the value was equal to or more than the reference value.
ALT	0-40	u/L	It was positive if the value was higher than the reference value.

**Table 2:** Comparison of general data among the three groups of pregnant women with high HBV load

Group	n	Age (Years)	Gravidity (times)	Parity (times)	Natural birth (n)	Cesarean section (n)
A	24	28.55±2.51	1.48±0.26	1.34±0.44	9	15
B	26	28.47±2.58	1.51±0.21	1.38±0.39	9	17
C	27	28.53±2.49	1.47±0.29	1.35±0.42	11	16
χ^2/t		0.075	0.384	0.231		0.104
P		0.940	0.707	0.819		0.764

Table 3: Levels of various markers at different times after TDF withdrawal in pregnant women in group A

Period (weeks)	ALT (μ /L)	HBV-DNA (cps/mL/mL)	HBeAg (PEIU/mL)	HBsAg (ng/mL)
2	16.24±3.28	723.23±97.67	0.31±0.12	0.23±0.12
4	17.24±3.44	624.76±82.34	0.39±0.08	0.37±0.05
8	17.13±3.21	783.67±93.24	0.37±0.06	0.33±0.12
12	16.33±3.64	874.56±90.23	0.38±0.04	0.41±0.03
18	17.45±3.57	821.38±84.35	0.34±0.14	0.26±0.10
24	17.39±3.45	838.94±92.45	0.33±0.09	0.27±0.13

Table 4: Levels of various markers at different times after TDF withdrawal in pregnant women in group B

Period (weeks)	ALT (μ /L)	HBV-DNA (cps/mL/mL)	HBeAg (PEIU/mL)	HBsAg (PEIU/mL)
2	17.09±3.11	821.39±84.57	0.32±0.12	0.34±0.08
4	17.21±2.87	568.92±95.67	0.35±0.13	0.35±0.12
8	16.54±2.75	689.23±96.11	0.37±0.06	0.37±0.08
12	16.27±3.19	763.22±95.33	0.29±0.18	0.42±0.02
18	17.03±3.43	873.67±93.29	0.30±0.06	0.38±0.04
24	17.36±3.14	792.38±95.66	0.33±0.17	0.28±0.11

Table 5: Levels of various markers at different times after TDF withdrawal in pregnant women in group C

Period (weeks)	ALT (μ /L)	HBV-DNA (cps/mL/mL)	HBeAg (PEIU/mL)	HBsAg (ng/mL)
2	19.12±2.94	735.67±89.03	0.30±0.08	0.30±0.05
4	19.33±2.42	835.24±94.66	0.28±0.12	0.37±0.03
8	19.21±3.19	683.67±84.19	0.36±0.11	0.39±0.06
12	18.55±3.04	679.22±86.45	0.34±0.10	0.40±0.08
18	17.14±3.12	745.35±88.21	0.31±0.14	0.34±0.12
24	17.27±2.84	851.27±92.37	0.29±0.15	0.31±0.09



Table 6: Success Rate of blockage of mother-to-child transmission of HBV among the three groups of pregnant women

Group	Immediately after delivery		At 1 month		At 6 months	
	HBV-DNA (+ve)	HBsAg (+ve)	HBV-DNA (+ve)	HBsAg (+ve)	HBV-DNA (+ve)	HBsAg (+ve)
A (n=24)	1 (4.17%)	1 (4.17%)	0	0	0	0
B (n=26)	0	0	0	0	0	0
C (n=27)	2 (7.41%)	2 (7.41%)	0	0	0	0
χ^2	1.116	1.116				
P-value	0.358	0.358				

Levels of various markers after TDF withdrawal in pregnant women in group C

As shown in Table 5, four markers returned to normal levels at different times after TDF withdrawal in group C.

HBV infection among the 3 groups of newborns

All the 83 newborns received injections of immunoglobulin and hepatitis B vaccine. The 83 neonates tested negative to HBV-DNA and HBsAg at 1 month after birth, with 100 % suppression of maternal transmission of HBV, and no HBV infection, as shown in Table 6.

Adverse reactions in three groups of parturient after medication

All the three groups of parturient women had adverse reactions after medication. There were 2 cases (8.33 %) of slight nausea, no vomiting, 1 case (4.17 %) of dizziness, and 1 case (4.17 %) of fatigue in group A. In group B, the numbers of cases of slight nausea, vomiting, dizziness and fatigue were 1 (3.85 %), 1 (3.85 %), 2 (7.69 %) and 1 (3.85 %), respectively, while the corresponding numbers in group C were 1 (3.70 %), 2 (7.41 %), 2 (7.41 %) and 0, respectively. Thus, the adverse reactions were mostly slight nausea and dizziness, which were tolerable, but no serious adverse reactions occurred. As shown in Figure 1, there were no significant differences in the incidence of adverse reactions among the three groups ($p > 0.05$).

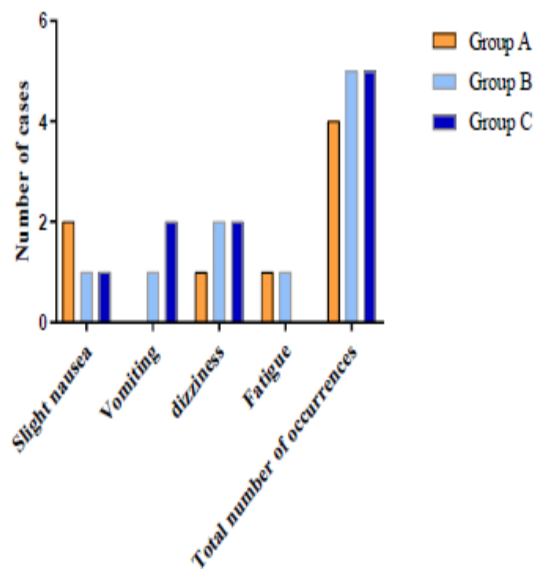


Figure 1: Comparison of adverse reactions in the three groups of parturient women after medication. Group A (drug discontinuation immediately after delivery); group B (drug discontinuation 1 month after delivery), and group C (drug discontinuation 3 months after delivery)

DISCUSSION

Hepatitis B virus (HBV) infection is a major transmissible disease which severely affects human health. It has been reported that about 1.7-1.9 billion people in the world have been infected with HBV, which has gradually developed into chronic HBV infection in 400 million patients [12]. There is a high incidence of HBV infection in China, with maternal transfer to fetus being the primary way of HBV



transmission. Therefore, investigations on effective ways of arresting maternal HBV transmission have become the focus of current medical research. Previous studies have reported the effectiveness of passive immunization of newborns in stopping HBV infection from maternal blood [13-15]. This immunization is mainly aimed at stopping infection of the baby with HBV from maternal source during or after childbirth, but it has no effective blocking impact on prenatal HBV infection.

The drug, TDF, a novel nucleotide reverse transcriptase inhibitor produced in the United States, blocks virus replication and transmission by inhibiting the activity of HIV-1 reverse transcriptase [16-18]. At present, the clinical effect of TDF in inhibiting HBV infection has been confirmed, and it has become the first choice of antiviral therapy for chronic HBV patients. Studies on HBV transmission have found that effective blocking of mother-to-child transmission has become the key to effective control of HBV infection. A study [19] has shown that the degree of maternal-to-neonatal infection in HBeAg-negative parturient women is significantly lower than that in those who are HBeAg-positive [19]. Thus, positive HBeAg is regarded as an important risk factor for intrauterine infection. Therefore, antiviral infection treatment is the predominant method used for arresting fetal transfer of HBV in third-trimester, high-load HBV-positive pregnant women. This study showed that the liver function and HBV markers returned to normal levels after TDF discontinuation for 2, 4, 8, 12 and 24 weeks in pregnant women who were receiving the drug at 24-28 weeks of gestation, suggesting that TDF was effective in these patients. Furthermore, pregnant women with high HBV load chose different TDF withdrawal times after delivery, which were the same as the times required for HBV-DNA to return to the levels before medication. In the literature [20], it was shown that the HBV-DNA contents in 35 pregnant women who received oral TDF for antiviral treatment at 24 - 28 weeks of gestation decreased by 2 - 4 log₁₀ values one month after treatment, relative to pre-therapy. Moreover, before delivery, viral DNA content in the treated women decreased significantly, when compared with that in parturient control. These results suggest that TDF exerts a strong antiviral influence. In this study, all three groups of parturient women had adverse reactions after medication, mainly slight nausea and dizziness, which were not severe reactions. In similar research on 30 parturient, high-load HBV women who received TDF antiviral treatment at 24 -

28 weeks of gestation, it was reported that during the treatment, 1 patient had slight nausea and 1 patient had limb weakness, which was tolerable, but no other serious adverse reactions occurred during pregnancy [21]. The present study showed that although TDF had high safety and low incidence of adverse reactions in patients, it also had certain impacts on mothers and infants. Therefore, in order for parturient women to breastfeed as early as possible after delivery so as to reduce the treatment costs, it is recommended that pregnant women with high HBV load should stop taking the drug immediately after delivery, to avoid prolonging the medication time.

Limitations of the study

This research has some limitations. For example, the small number of samples selected, and the short study time may lead to some deviations from the results reported.

CONCLUSION

Withdrawal of TDF immediately after delivery or 1 - 3 months after delivery, has no effect on biochemical analyses of HBV and viral transmission in pregnant women with high HBV load who took TDF during late pregnancy period. However, discontinuing TDF is recommended for pregnant women immediately after delivery, considering breastfeeding, occurrence of adverse reactions and treatment costs. It is necessary to increase the number of samples in subsequent studies in order to validate the research results.

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