Hepatology International
https://doi.org/10.1007/s12072-022-10412-w

ORIGINAL ARTICLE

E□ects of antiviral therapy and drug withdrawal on postpartum hepatitis in pregnant women with chronic HBV infection

Minghui Li[1,2] · Fangfang Sun[1] · Xiaoyue Bi[1] · Yanjie Lin[2] · Liu Yang[1] · Tingting Jiang[1] · Wen Deng[1] · Yao Lu[1] · Lu Zhang[1] · Wei Yi[3] · Yao Xie[1,2]

Received: 3 June 2022 / Accepted: 13 August 2022

Abstract

Objective To investigate the effect of antiviral therapy and drug withdrawal on the incidence of hepatitis B after delivery in pregnant women with chronic hepatitis B virus (CHB) infection who received tenofovir disoproxil fumarate (TDF) treatment.

Methods

Published online: 15 September 2022

pregnant women are reluctant to take antiviral drugs because of concerns about the safety of breastfeeding. A considerable proportion of patients with chronic HBV infection have postpartum hepatitis after delivery, with a proportion as high as 50% [11], especially within 6 months after delivery [12], and some patients present with severe chronic hepatitis B and liver failure [13]. Our previous findings suggest that HBV DNA positivity at delivery and postpartum alanine aminotransferase (ALT) elevation in chronic HBV infection patients without antiviral therapy are independent predictors of acute exacerbation of chronic hepatitis B [14]. However, the predictors of acute exacerbation of chronic hepatitis B after short-term antiviral therapy in pregnant women with chronic HBV infection are still limited. Whether withdrawal of antiviral therapy after delivery will affect the occurrence of postpartum hepatitis is unclear. In this study, we observed the incidence of postpartum hepatitis in pregnant women with chronic HBV infection who were treated with or without antiviral drugs, and explored the impact of different timing of stopping antiviral treatment on the occurrence of hepatitis after delivery.

Some studies reported the recurrence of postpartum hepatitis in patients with chronic HBV infection, focusing on the blocking effect of antiviral therapy during pregnancy on mother-to-child transmission of HBV [15–19]. In these studies, inconsistent timing of postpartum drug discontinuation among pregnant women might influence the development of postpartum hepatitis [15–19]. We published a large sample retrospective study in 2018 showing that abnormal postnatal liver function was common in both non-HBV-infected and HBV-infected women, and abnormal postnatal liver function in HBV-infected women occurred in those with viral load greater than 10^6 IU/ml [14]. Currently, there are few studies on the occurrence and influencing factors of postpartum hepatitis in pregnant women with chronic HBV infection. In this prospective study, we studied the occurrence of postpartum hepatitis in untreated pregnant women with chronic HBV infection, pregnant women who received TDF treatment for the prevention of mother-to-child transmission of HBV during pregnancy and stopped treatment immediately after delivery or 6 weeks after delivery. The results will more accurately reveal the effect of TDF treatment and drug withdrawal during pregnancy on the occurrence of postpartum hepatitis.

Patients and methods

Subjects and study design

This is a prospective observational cohort study of HBeAg-positive and HBV-DNA positive pregnant women. Eligible mothers with chronic HBV infection who underwent prenatal examination and delivered at Beijing Ditan Hospital between January 1, 2017 and December 30, 2019 were enrolled. This study was approved by the Ethics Committee of Beijing Ditan Hospital Affiliated to Capital University of Medical Sciences (Jing Di Lun Ke Zi 2017 No. 004-02), and was registered with Clinical Trials (NCT03214302).

Inclusion criteria were: HBeAg positive and HBV DNA $> 10^6$ IU/ml; No anti HBV drugs were taken before entering the group; No pregnancy induced hypertension, premature rupture of membranes, prenatal bleeding and other diseases; No history of amniocentesis during pregnancy; No other

reagent. The detection range of HBsAg level was 0.05–250 IU/ml. If the HBsAg level was greater than 250 IU/ml, it'd be automatically diluted 500 times. The actual HBsAg level was calculated by multiplying the test value by 500. HBsAg < 0.0 5 IU/ml was defined as the disappearance of HBsAg.

Statistical analysis

The continuous variables were described by mean, standard deviation, maximum, minimum, median and interquartile range. The classified data are statistically described by frequency and rate. Chi-square analysis, Fisher test, *t* test and Wilcoxon nonparametric test were used for comparison between groups.

Chi-square test, Mantel–Haenszel hierarchical analysis, trend chi-square analysis, and analysis of covariance were used to find the correlation with the occurrence of hepatitis after drug withdrawal.

Because there are many factors affecting the failure of HBV mother-to-child transmission interruption and the occurrence of hepatitis after delivery, unconditional logistic regression analysis was conducted, in which the success of HBV mother-to-child transmission interruption or the occurrence of hepatitis is taken as the dependent variable, and study factors are taken as the independent variables. Stepwise regression method was used for variable selection.

Results

Patient enrollment and deposition

A total of 397 HBeAg-positive pregnant women with chronic HBV infection and age 30.74 ± 3.85 years were enrolled during the study, of whom 112 received no antiviral treatment (Control gre no anti

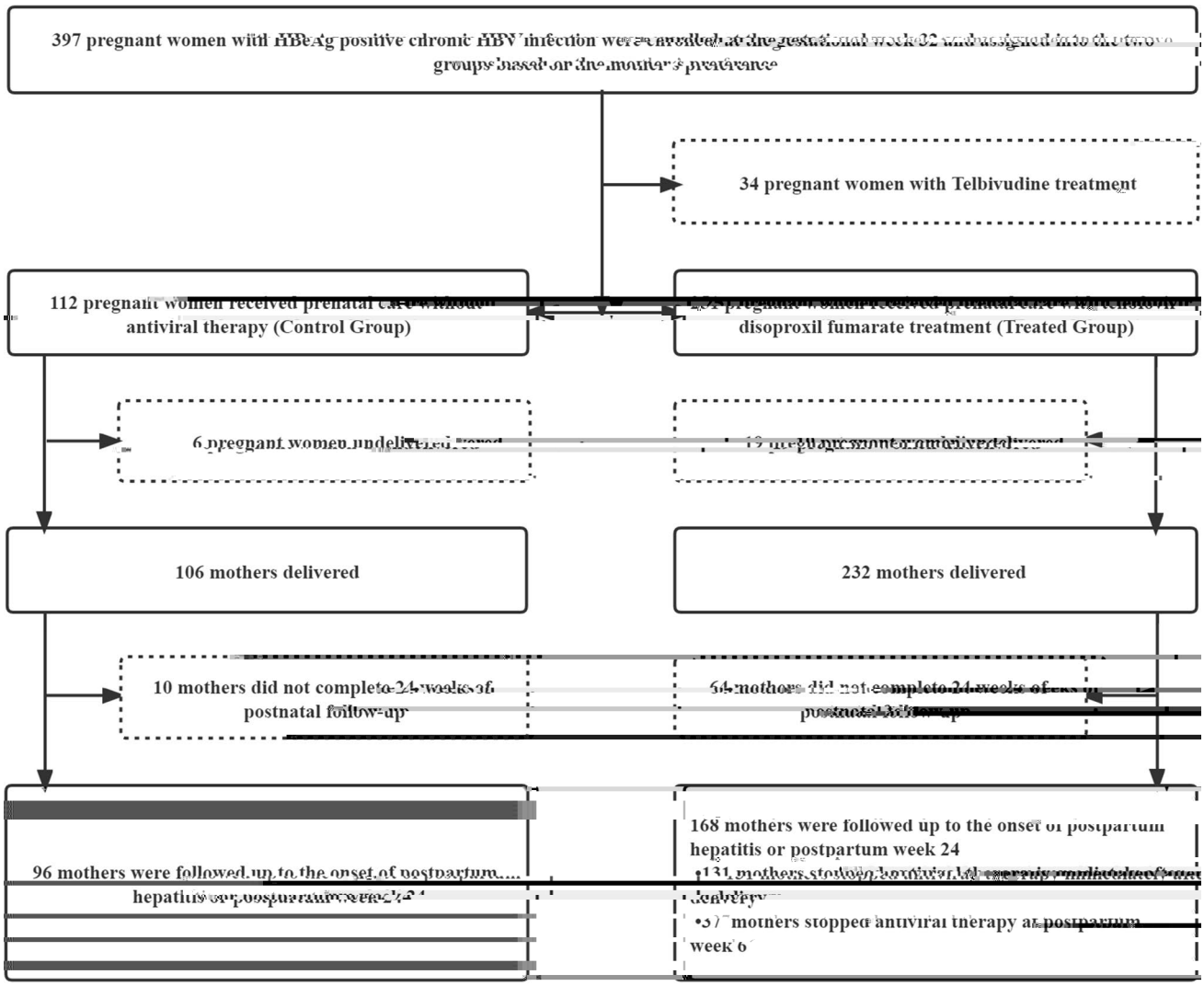

Fig. 1 Patient enrollment and deposition

treated with TDF and 28 patients treated with PEG-IFN or PEG-IFN combined with TDF.

The results of logistic regression analysis showed that the occurrence of hepatitis after delivery was not related to the patient's age, antiviral treatment, DNA content before enrollment and before delivery, and whether to stop antiviral drug immediately (Table 5).

HBV markers at birth and blocking effect of HBV mother-to-child transmission in newborns

A total of 346 newborns were delivered, including 189 males and 157 females, with body length 50.07 ± 1.07 cm, weight 3311.78 ± 424.04 g, Apgar1 score 9.97 ± 0.26, Apgar 5 score 9.99 ± 0.22, Apgar 10 score 10.00 ± 0.00. There were 7 cases of fetal malformation, including 5 cases of syndactyl, 1 case of genital malformation and 1 case of cryptorchidism. In 326 patients who obtained HBV serum markers in venous blood at birth, 41.4% (135) were HBsAg positive (HBsAg > 0.05 IU/ml) and HBsAg level was 0.14 (0.08, 0.41) IU/ml. 96.3% (314) were HBeAg positive (HBeAg > 1.0 S/CO), the HBeAg level was 64.46(18.15, 169.72) S/CO. 98.5% were anti-HBe negative (anti-HBe > 1.0 S/CO). 98.5% (321) were anti-HBc positive (anti-HBc > 1.0 S/CO). Serum HBV DNA content was detected in 321 cases, 14.0% positive (HBV DNA ≥ 20 IU/ ml), and HBV DNA content was 3.47 ± 1.33 log IU/ml.

Table 1 Clinical biochemical parameters during pregnancy

	Baseline enrollment (31–32 weeks of gestation)				After enrollment (antiviral therapy 4 w)				Before delivery			
	Control	Treated	*T* test	*p* value	Control	Treated	*T* test	*p* value	Control	Treated	*T* test	*p* value
Age(years)	29.99 ± 3.60	31.35 ± 3.95	2.805	0.005	/	/	/	/	/	/	/	/
HBV DNA (log_{10} IU/mL)	7.99 ± 0.62	8.03 ± 0.51	0.676	0.500	7.55 ± 0.80	5.20 ± 0.72	–9.910	< 0.001	7.87 ± 1.20	4.50 ± 1.03	–23.928	< 0.001
HBeAg–positive, %	100%	100%	–	–	100%	100%			100%	100%		
ALT (U/L)	22.17 ± 14.80	23.46 ± 20.03	0.051	0.960	20.71 ± 27.69	23.75 ± 18.81	1.050	0.295	18.41 ± 11.80	20.30 ± 9.73	1.770	0.078
AST (U/L)	21.60 ± 14.61	22.44 ± 6.21	0.239	0.812	20.85 ± 13.03	23.63 ± 11.04	2.091	0.038	21.47 ± 9.22	22.72 ± 6.29	2.105	0.036
TBIL (μmol/L)	7.11 ± 2.41	7.74 ± 2.59	1.909	0.057	7.62 ± 3.44	7.99 ± 2.56	0.932	0.352	7.29 ± 2.68	7.48 ± 2.66	0.321	0.748
DBIL (μmol/L)	1.72 ± 0.76	1.771.23	0.157	0.875	1.70 ± 1.03	1.91 ± 0.87	1.396	0.164	1.68 ± 1.26	1.72 ± 0.82	0.062	0.951
ALB (g/L)	39.03 ± 3.28	37.09 ± 2.07	–5.525	< 0.001	36.75 ± 2.44	36.24 ± 2.66	–2.714	0.008	35.77 ± 2.86	35.86 ± 3.06	–0.446	0.656
GGT (U/L)	10.15 ± 7.81	9.60 ± 6.73	–0.957	0.339	9.79 ± 6.77	9.37 ± 5.61	–0.997	0.320	10.06 ± 5.47	9.29 ± 4.86	–0.273	0.786
ALP (U/L)	70.55 ± 34.25	76.80 ± 23.13	1.600	0.112	129.88 ± 52.41	149.66 ± 346.69	0.607	0.545	140.52 ± 32.73	159.07 ± 51.51	1.797	0.078
TBA (μmol/L)	3.25 ± 2.60	4.11 ± 8.91	0.531	0.596	3.70 ± 3.35	7.66 ± 41.40	0.902	0.368	8.90 ± 7.71	78.36 ± 536.73	–1.155	0.253
BUN (μmol/L)	3.08 ± 0.78	3.96 ± 11.64	0.662	0.509	2.92 ± 0.62	3.10 ± 0.80	0.994	0.321	3.91 ± 3.35	3.64 ± 0.90	–1.147	0.252
Cr (μmol/L)	44.33 ± 5.78	45.63 ± 11.95	0.530	0.597	46.67 ± 5.19	50.90 ± 23.20	0.890	0.375	50.53 ± 8.63	55.51 ± 41.58	1.166	0.245
PHOS (mmol/L)	1.11 ± 0.10	1.18 ± 0.65	0.865	0.388	1.15 ± 0.13	1.13 ± 0.13	–1.075	0.284	1.13 ± 0.15	1.10 ± 0.17	–1.382	0.168
PTA (%)	109.99 ± 13.45	113.40 ± 10.34	2.089	0.041	116.68 ± 9.95	116.79 ± 10.59	0.102	0.919	117.03 ± 17.82	111.41 ± 15.73	–2.732	0.007
INR	0.97 ± 0.05	1.35 ± 6.00	0.498	0.619	0.96 ± 0.05	0.93 ± 0.05	–2.019	0.045	0.94 ± 0.04	0.96 ± 0.06	0.743	0.458

Notes: HBV DNA: hepatitis B virus deoxyribose nucleic acid; HBeAg: hepatitis B e antigen; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBil: total bilirubin; DBil: direct bilirubin; ALB: Albumin; GGT: glutamyl transpeptidase; ALP: alkaline phosphatase; TBA: total bile acid; BUN: urea nitrogen; Cr: creatinine; PHOS: phosphorus; PTA: prothrombin time activity; INR: international normalized ratio

Table 2 HBV DNA levels in HBV-positive patients during pregnancy and after delivery

HBV DNA level (log_{10} IU/mL)	Control	Immediate withdrawal	Delayed withdrawal	*T* test/*p* value Control vs. Immediate withdrawal	*T* test/*p* value Control vs. Delayed withdrawal	*T* test/*p* value Immediate withdrawal vs. Delayed withdrawal
Before antiviral therapy	7.99 ± 0.62	8.05 ± 0.51	7.98 ± 0.52	–0.708/0.479	0.077/0.939	0.648/0.518
4 weeks after antiviral therapy	7.55 ± 0.80	5.24 ± 0.62	5.21 ± 0.94			

Notes: Control: no antiviral treatment during pregnancy

Immediate withdrawal: withdrawal of antiviral drugs immediately after delivery

Delayed withdrawal: withdrawal of antiviral drugs at 6 weeks after delivery

All newborns in this study received anti-HBV HBIG 100 IU injection and 10 μg hepatitis B vaccine within 6 hours after birth, and returned to the community to receive hepatitis B vaccine at 1 and 6 months after birth. In this study, a total of 262 newborns received the follow-up results of blocking HBV mother-to-child transmission, and the success rates of blocking was significantly different in the treatment group (155/156, 99.35%) and the control group (96/106, 90.56%)(χ^2=12.132, $p < 0.001$).

Discussion

Guidelines recommend short-course antiviral therapy to reduce the risk of mother-to-child transmission of chronic hepatitis B virus in pregnant women with high viral load [5, 8–10, 23]. Unfortunately, some patients have postpartum chronic hepatitis B after the end of short-course antiviral therapy. The aim of the study was to examine the timing of

Table 3 Incidence of postpartum hepatitis in different population groups

	Control ($n=96$)	Immediate withdrawal ($n=131$)	Delayed withdrawal ($n=37$)	χ^2/p value control vs. immediate withdrawal	χ^2/p value control vs. delayed withdrawal	χ^2/p value immediate withdrawal vs. delayed withdrawal	χ^2/p value Control vs. Treated
Incidence of hepatitis% (n)	28.1% (27)	23.7% (31)	24.3% (9)	0.580/0.446	0.195/0.658	0.007/0.934	0.601/0.438

Notes: Control: no antiviral treatment during pregnancy
Immediate withdrawal: withdrawal of antiviral drugs immediately after delivery
Delayed withdrawal: withdrawal of antiviral drugs at 6 weeks after delivery

drug withdrawal on occurrence of hepatitis after delivery in pregnant women with chronic HBV infection.

Antiviral therapy during pregnancy is an important measure to improve the blocking rate of mother-to-child transmission of HBV. However, HBV infected pregnant women with significant hepatitis, liver fibrosis or cirrhosis during pregnancy must continue antiviral therapy even after delivery, so we excluded these patients from our study [20, 21, 24, 25]. Currently, there is no consensus on when to stop antiviral drugs after delivery and its effect on the occurrence of postpartum hepatitis in these pregnant women who take antiviral drugs during pregnancy to prevent mother-to-child transmission of HBV [20, 21, 24, 25]. The aim of this study was to investigate the effect of withdrawal of TDF after delivery on the occurrence of postpartum hepatitis and hepatitis development in pregnant women who had been using TDF for prevention of HBV mother-to-child transmission during pregnancy, thus HBV-infected pregnant women with significant hepatitis, liver fibrosis or cirrhosis during pregnancy were excluded. Meanwhile, in order to reduce the pregnancy complications (such as gestational hypertension) and delivery complications (such as postpartum hemorrhage) on the safety of TDF use, occurrence of postpartum hepatitis and deterioration of liver function, patients with gestational hypertension, premature rupture of membranes, prenatal bleeding and other pregnancy and/or delivery complications were excluded in this study. Patients with other causes of liver disease, liver fibrosis and cirrhosis were also excluded. Adverse reactions, especially renal impairment, were closely monitored during TDF antiviral therapy.

TDF is recommended as the first choice for preventing mother-to-child transmission of HBV because it can effectively inhibit HBV replication, with little drug resistance and high safety in pregnancy [25, 26]. Studies have shown that on the basis of regular neonatal immunization, if the serum HBV DNA of pregnant women was reduced to 10^6 IU/ ml before delivery, the mother-to-child transmission of HBV could be effectively blocked [27–30]. Some studies did not recommend antiviral therapy during pregnancy for blocking mother-to-child transmission of HBV in pregnant women with HBVDNA $< 10^6$ IU/ml [31]. Although most current guidelines recommend antiviral therapy for prevention of mother-to-child transmission of HBV from 28 weeks of gestation, TDF can reduce HBV DNA by more than 3 log (HBV DNA $< 10^6$ IU/ml) in pregnant women after 4 weeks of treatment due to its strong inhibition of virus replication [32]. To minimize the risk of fetal exposure to TDF and reduce the side effects of drugs on pregnant women, antiviral therapy was started at 32 weeks of gestation in this study.

Our study results showed that the success rate of mother-to-child block in tenofovir group at 32 weeks of gestation was 99.35%, which was significantly higher than that in Control group (90.56%). At the same time, HBV DNA

levels were signifi antly lower in the treated group at 4 weeks of antiviral treatment and before delivery than those in the untreated group, suggesting that tenofovir dipivoxil has a good antiviral effe t [23, 33]. Our study showed that HBV DNA remained at a relatively stable high level during pregnan y and after delivery in the Control group. After 4 weeks of treatment, HBV DNA was signifi antly redu ed in the tenofovir group, and the virus qui kly rebounded to a high level after 6 weeks of withdrawal. But there was still a de rease in HBV DNA levels after delivery ompared with baseline, whi h was asso iated with the o urren e of hepatitis in some patients. Be ause the high estrogen and progesterone of pregnant women an inhibit the fun tion of immune ells of pregnant women, the immunity against HBV an also be inhibited during pregnan y. After delivery, due to the de rease of hormone levels, the inhibition of immune fun tion is relieved, thus indu ing the immune response to HBV, ausing damage to liver tissue and leading to the o urren e of hepatitis.

In this prospe tive study, the in iden e of postpartum hepatitis B in HBeAg-positive pregnant women with hroni a high lein the untreated group, suo thu T]TJ-.002 5(( )]%- de %)-26(r)25.]T

during pregnancy, HBV DNA level before delivery and the time of drug withdrawal.

In conclusion, withdraw of antiviral treatment immediately or at 6 weeks after delivery did not affect the incidence of hepatitis after delivery. Above 90% of hepatitis occurred within 12 weeks after delivery in those without antiviral treatment and who immediately stopped antiviral treatment after delivery. Delaying drug withdrawal might delay the onset of postpartum hepatitis. Our results also suggest that postpartum or 12 weeks after drug withdrawal is the key follow-up period to monitor the occurrence of hepatitis. However, due to the number of completed follow-up subjects is limited in this study, the conclusions need to be further verified. What's more, because monitoring for only 24 weeks after delivery may overlook the incidence of late flare, it's recommended to observe the incidence of hepatitis at 48 weeks of postpartum in future studies.

Acknowledgements The authors thank all study patients and staffs participating in the study.

Author contributions ML and YX contributed to the study design and the data analysis. ML, WY, and YX contributed to the recruitment, enrolment, and assessment of participants, as well as data collection. LZ, YL, FS, YL, LY, and WD contributed to following up with the patients. XB, TJ, and LY managed all aspects of laboratory support.

20. Chinese Society of Infectious Diseases CMA, Chinese Society of Hepatology CMA. The guidelines of prevention and treatment for chronic hepatitis B. version). Zhonghua Gan Zang Bing Za Zhi. 2019;2019(27):938–961
21. Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH, American Association for the Study of Liver D. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016;63:261–283.
22. Tan HH, Lui HF, Chow WC. Chronic hepatitis B virus (HBV) infection in pregnancy. Hepatol Int. 2008;2:370–375
23. Chen R, Zou J, Long L, Huang H, Zhang M, Fan X, et al. Safety and efficacy of tenofovir alafenamide fumarate in early-middle pregnancy for mothers with chronic hepatitis B. Front Med (Lausanne). 2021;8: 796901
24. Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int. 2016;10:1–98
25.