Efficacy and Safety of Telbivudine in Preventing Mother-to-Child Transmission of Hepatitis B Virus

Tongtong Chen

Hangzhou Xixi Hospital Affiliated to Zhejiang Chinese Medical University

Yunlei Xiao

Hangzhou Xixi Hospital Affiliated to Zhejiang Chinese Medical University

Chun Zhao

Hangzhou Xixi Hospital Affiliated to Zhejiang Chinese Medical University

Xiaoxian Chen

Maternal and child health hospital of Tonglu, Hangzhou

Shourong Liu (✉ lsh85463990@126.com)

Hangzhou Xixi Hospital Affiliated to Zhejiang Chinese Medical University

Research Article

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Abstract

Background: To define the best timing for the treatment of high maternal viral DNA levels in order to block the mother-to-child transmission (MTCT).

Methods: From a total of 820 HBsAg-positive pregnant women, 229 who satisfied the selection criteria were enrolled for the final analysis. These patients were divided into three groups: Group A: 62 patients received telbivudine (LdT) (600 mg/day, orally) treatment before pregnant; Group B: 101 patients received LdT treatment at 24-28 weeks of gestation; and Group C: 66 patients with high viral load received LdT at the third trimester. All infants born to the enrolled women were vaccinated with 100 IU of hepatitis B immune globulin (HBIG) and 10 µg of hepatitis B vaccine within 2 hours of birth. The second and third doses of recombinant HBV vaccine were administered at 1 and 6 months of age, respectively.

Results: LdT can effectively reduce serum HBV DNA and normalize ALT levels before delivery ($p < 0.001$). The HBsAg positivity rate in infants in Groups A, B and C after delivery was 1.6%, 7.9% and 3.0%, respectively. The serum HBV DNA positivity rate in infants in Groups A, B and C after delivery was 4.8%, 5.0% and 0%, respectively. After 28 weeks of follow up, all infants remained HBV DNA and/or HBsAg negative. No serious adverse events were found in the mothers or their infants treated with LdT.

Conclusions: Telbivudine (LdT) given at the 28-32 weeks of gestation can effectively reduce mother-to-child transmission in HBV-infected women with good safety.

Introduction

Globally, hepatitis B virus (HBV) infection is still a serious public health issue affecting over 240 million people.^[1, 2] China has the greatest number of HBV surface antigen (HBsAg) positive population.^[3] Mother-to-child transmission (MTCT) and perinatal transmission are among the major modes of HBV spread in young children. HBV vaccine combined with hepatitis B immune globulin (HBIG) has been shown to reduce the rates of MTCT. Without intervention, 80–90% of infants born to mothers who are positive for HBV e antigen (HBeAg) will be infected with HBV. The combination of passive and active immunization after birth reduces the rates of MTCT from 90–10%.^[4, 5] At present in China, over 90% of infants receive birth-dose vaccination.^[3] However, there is still a risk of failure in immunization prevention. In a previous study from China, the rate of immunoprophylaxis failure in infants born to HBV DNA positive mothers whose HBV DNA levels ranged at < 6 , $6-6.99$, $\geq 7 \log_{10}$ copies/ml were 0%, 10.1% and 12.1%, respectively.^[6] Hence, higher HBV DNA level in mothers is associated with higher level of transmission. In addition to the high maternal HBV-DNA load, other factors including positive HBeAg, intrauterine infection and viral mutation also contribute to the higher level of viral transmission to infants. Pregnant women with high HBV replication levels are associated with higher risk of HBV MTCT.^[5-7] In the combined immunization program, 10–30% of the infants born to mothers whose viral DNA levels were $> 10^6$ copies/mL and were positive for HBeAg experienced immunoprophylaxis failure whereas only 3% of infants born to mothers whose serum viral loads were $< 10^6$ copies/mL had immunoprophylaxis failure.^[8]

In all pregnant women with high HBV DNA levels ($> 200,000$ IU/ml), tenofovir (TDF), telbivudine (Ltd.) and Lamivudine (LAM) were recommended to block vertical transmission of HBV.^[1, 2] Ltd. is a class B drug approved by the US Food and Drug Administration for the treatment of adult patients with CHB,^[9] and its safety and effectiveness in blocking MTCT of HBV have been confirmed in many studies.^[4, 10–12] According to the guidelines of the Asian Pacific Association for the Study of the Liver, Ltd. can be used as a replacement antiviral agent during pregnancy.^[9] However, the suitable time to perform antiviral therapy still controversial.

In this study, we aimed to evaluate the best timing to initiate the Ltd treatment in the pregnant women who were HBeAg positive and had high viral DNA levels, and assess the effectiveness for MTCT prevention, HBV DNA suppression, maternal and infant safety.

Patients And Methods

Patients selected

This is a retrospective cohort study and the patients included in this study were recruited from Xixi Hospital of Hangzhou between January 2014 and March 2018. The study was approved by the Ethics Committee of the Xixi Hospital. The data are anonymous, and the requirement for informed consent was therefore waived by Ethics Committee of Xixi Hospital of Hangzhou. CHB diagnosis was diagnosed according to the Guideline of Prevention and Treatment for Chronic Hepatitis B (2019 Update).

The inclusion criteria were as follows: (1) women aged between 20 to 40 years old; (2) confirmed pregnancy; (3) HBsAg positive and HBeAg positive (prior to seroconversion); (4) HBV DNA level $\geq 5 \log_{10}$ copies/mL; or (5) viral load of > 20000 IU/mL and elevated alanine aminotransferase level (ALT, > 40 U/L). The exclusion criteria were as follows: (1) history of a child birth with immunoprophylaxis failure; (2) preterm labor; (3) co-infection with hepatitis A, C, D, E, or HIV virus; (4) fetal malformations found by ultrasound examination; and (5) treatment with HBIG during pregnancy.

Patient Grouping And Management

Treatment group ($n = 128$): patients received 600 mg/day LdT (orally, Novartis, Swiss) at pregestation (Group C, $n = 62$) and the week 28 to week 32 of gestation (Group B, $n = 66$). Control group (Group A, $n = 101$): patients received 600 mg/day LdT (orally, Novartis, Swiss) at week 24 to week 28 of gestation. LdT was stopped if the patients were in immune tolerant phase (i.e., with normal serum ALT) after one month of postpartum. LdT was continued in patients with abnormal baseline serum ALT levels (> 40 U/L).

All infants born to the enrolled women were vaccinated with 100 IU of hepatitis B immune globulin (HBIG) and 10 μ g of hepatitis B vaccine within 2 hours postpartum. The second and third doses of recombinant HBV vaccine were administered at 1 and 6 months of age, respectively.

Outcome Assessment

The primary outcome was the MTCT rate. The MTCT rates were compared between the treatment group and the control group. The MTCT rate was defined by HBsAg seropositivity or HBV DNA positivity at 4–7 months postpartum.

The secondary outcomes include (1) maternal HBV DNA levels before delivery; (2) maternal complications during the prenatal period, including gestational diabetes mellitus (GDM), hypertensive disorder complicating pregnancy (HDCP), intrahepatic cholestasis of pregnancy (ICP), premature rupture of membranes, hypothyroidism, postpartum hemorrhage, meconium staining of the amniotic fluid, and fetal distress; and (3) infant outcomes such as gestational age, weight, Apgar score, and birth defect rates.

Virology Tests

HBV serological markers (HBsAg, anti-HBs, HBeAg, anti-HBe, and anti-HBc) were measured using a chemiluminescent microparticle immunoassay (Architect i2000 Analyzer; Abbott Diagnostics, USA). Serum HBV DNA levels were determined using a real-time polymerase chain reaction (PCR) system (Shanghai Hongshi Medical Technology Co., Ltd.), with a lower detection limit of 30 IU/mL.

Statistical Methods

Continuous variables were expressed as mean $\pm$ standard deviation (SD) and categorical values were expressed by absolute and relative frequencies. Differences of continuous data between groups were analyzed by Mann-Whitney U test or one-way ANOVA. The *Chi*-square test or the Fisher's exact test was used for categorical data as appropriate. A $p < 0.05$ was considered statistically significant. Statistical analysis were performed using the SPSS19.0 (SPSS, Inc., Chicago, IL).

Results

Baseline characteristics of pregnant women and newborns

A total of 820 HBsAg-positive pregnant women were enrolled, and 229 were included in the final analysis. The patients were grouped by the timing of LdT treatment. Hence, 62 patients were given LdT before pregnant and designated as Group A; 101 patients were given LdT at 24–28 weeks of gestation, and designated as Group B (control group); and 66 patients with high viral load were given LdT at the 28 to week 32 of gestation (third trimester), and designated as Group C. Their clinical characteristics are shown in Table 1.

Table 1
Characteristics of pregnant women and newborn infants from group A, B and C

Variab	Group A (62)	group B (101)	group C (66)	F/ χ^2	P value
Age(years)	29.11 $\pm$ 3.42	28.95 $\pm$ 3.91	27.91 $\pm$ 3.01	2.827	0.063
Delivery method				0.919	0.632
Vaginal delivery	33	60	40		
Cesarean delivery	29	51	26		
Weight (kg)	68.15 $\pm$ 8.58	66.81 $\pm$ 8.77	66.61 $\pm$ 8.60	0.623	0.538
Height (cm)	160.37 $\pm$ 0.67	159.68 $\pm$ 0.50	156.74 $\pm$ 2.04	1.507	0.226
Baseline HBV DNA (log 10 IU/ml)	7.10 $\pm$ 0.82	7.35 $\pm$ 0.83	7.22 $\pm$ 0.80	1.838	0.162
HBeAg (Log 10 S/CO)	2.50 $\pm$ 0.88	2.77 $\pm$ 0.75	2.74 $\pm$ 0.72	2.451	0.089
ALT (U/L)	37.60 $\pm$ 26.01	38.58 $\pm$ 30.67	33.91 $\pm$ 23.21	0.601	0.549
AST (U/L)	33.26 $\pm$ 26.73	33.75 $\pm$ 29.57	38.70 $\pm$ 29.95	0.744	0.476
ALP (U/L)	233.44 $\pm$ 84.71	233.85 $\pm$ 87.04	219.77 $\pm$ 77.78	0.648	0.524
GGT (U/L)	17.27 $\pm$ 9.49	20.44 $\pm$ 12.98	17.53 $\pm$ 9.77	2.059	0.130
Hb (g/L)	119.68 $\pm$ 22.24	119.04 $\pm$ 13.35	113.89 $\pm$ 19.09	2.175	0.116
Tb (μ mol/L)	9.28 $\pm$ 2.71	9.79 $\pm$ 3.46	8.66 $\pm$ 2.16	2.971	0.053
Glycocholic acid (mg/L)	2.53 $\pm$ 1.50	2.46 $\pm$ 1.88	2.56 $\pm$ 1.93	0.076	0.927
Creatinine (μ mol/L)	50.26 $\pm$ 9.47	49.56 $\pm$ 8.10	50.24 $\pm$ 11.16	0.149	0.862
TP (g/L)	64.04 $\pm$ 5.34	63.58 $\pm$ 4.35	63.86 $\pm$ 5.57	0.177	0.838
Alb (g/L)	34.44 $\pm$ 3.60	34.64 $\pm$ 2.92	24.15 $\pm$ 2.50	0.534	0.587
PT (s)	11.55 $\pm$ 0.79	11.55 $\pm$ 0.73	11.72 $\pm$ 0.76	1.242	0.291
Gestational age at birth (weeks)	39.51 $\pm$ 0.93	39.33 $\pm$ 1.07	39.47 $\pm$ 0.91	0.728	0.484
Weight (kg)	3.33 $\pm$ 0.56	3.32 $\pm$ 0.44	3.31 $\pm$ 0.53	0.022	0.978
Apgar score	9.94 $\pm$ 0.25	9.85 $\pm$ 0.64	9.71 $\pm$ 1.02	1.985	0.142
Continuous variables were expressed by mean $\pm$ SD and categorical values were described by count and proportions.					

As shown in Table 1, the baseline demographics and clinical characteristics were similar between the treatment and control groups.

Efficacy of LdT on the virology and liver function tests in mothers

Baseline serum HBV DNA levels were similar across the three groups (7.10 ± 0.82 in Group A, 7.35 ± 0.83 log 10 IU/ml in Group B, and 7.22 ± 0.80 log 10 IU/ml in Group C, $p > 0.05$). The HBV DNA levels decreased significantly in all groups following LdT treatments ($p < 0.001$) with the similar extent ($p > 0.05$) (all compared to each group). (Table 3).

Table 2

Comparison of perinatal complications of pregnant mothers infected with hepatitis B virus from group A, B and C.

Variables	group A (62)	group B (101)	group C (66)	F/ χ^2	P value
perinatal complications	20	35	16	2.085	0.353
Intrahepatic cholestasis	2	6	1		
Hypothyroidism	2	7	0		
Premature rupture of membrane	6	6	11	1.756	0.416
Fetal distress	2	5	0		
Postpartum hemorrhage	0	2	1		
Eclampsia	0	3	0		
Pregnancy-induced hypertension	2	0	1		
perinatal complications include Intrahepatic cholestasis, Hypothyroidism, Premature rupture of membrane, Fetal distress, Postpartum hemorrhage, Eclampsia and Pregnancy-induced hypertension.					

Table 3
Change of HBV DNA level, ALT and AST after LdT treatment in pregnant women

	group A(62)	group B(101)	group c(66)	F	P value
HBV DNA					
Baseline	7.10 ± 0.82	7.35 ± 0.83	7.22 ± 0.80	1.838	0.162
Before delivery	3.94 ± 2.12*	4.44 ± 2.43*	4.79 ± 2.22*	2.218	0.088
Postpartum 28 weeks	6.16 ± 1.42#*	6.58 ± 1.51#*	6.49 ± 1.65#*	1.496	0.226
ALT					
Baseline	37.60 ± 26.01	38.58 ± 30.67	33.91 ± 23.21	0.601	0.549
Before delivery	23.37 ± 14.81*	25.43 ± 13.05*	22.82 ± 13.24*	0.862	0.424
AST					
Baseline	33.26 ± 26.73	33.75 ± 29.57	38.70 ± 29.95	0.744	0.476
Before delivery	27.53 ± 12.89	30.30 ± 12.85	28.44 ± 14.47*	0.91	0.404
CK(U/L)					
Before delivery	88.66 ± 59.26	99.86 ± 47.89	81.74 ± 63.19	2.225	0.110
*means that Before delivery compared to Baseline statistically significant ($p < 0.001$). #means that Before Postpartum 28 weeks compared to Baseline statistically significant ($p < 0.001$).					

No significant difference in ALT and AST levels was found among each group before LdT treatment ($p > 0.05$) (Table 3). In all three groups, treatment with LdT led to a significant reduction of serum ALT levels ($p < 0.001$, respectively). At 28 weeks postpartum, there was no significant difference in the level of serum HBV DNA ($p > 0.05$, respectively).

Efficacy of LdT on the virology and liver function tests in newborns

The rates of HBsAg positivity in the infants of Groups A, B and C were 1.6% (1/62), 7.9% (8/101) and 3.0% (2/66), respectively (Table 4). The rates of serum HBV DNA positivity in the infants of Groups A, B and C were 4.8% (3/62), 5.0% (5/101) and 0% (0/66), respectively (Table 4). A total of 16 newborns were positive for hepatitis B surface antigen and/or HBV DNA. Among them, three infants in group B are positive for HBV DNA and HBsAg. 28 weeks after birth, all infants were negative for HBV DNA and/or HBsAg.

Table 4
Hepatitis B surface antigen and HBV DNA of infants after birth from group A, B and C.

Positive			Negative	
group A(62)				
HBsAg	1 (1/62)	1.60%	61 (61/62)	98.40%
HBV DNA	3 (3/62)	4.80%	59 (59/62)	95.20%
group B(101)				
HBsAg	8 (8/101)	7.90%	93 (93/103)	92.10%
HBV DNA	5 (5/101)	5.00%	96 (96/101)	95.00%
group c(66)				
HBsAg	2 (2/66)	3.00%	64 (64/66)	97.00%
HBV DNA	0 (0/66)	0.00%	66 (0/66)	100.00%

Maternal And Infant Safety

There were no significant differences in neonatal gestational age, weight at birth, Apgar score or neonatal deformities among the infants in the three groups (Table 1). There were no significant differences in the overall incidence of adverse pregnancy events (including premature rupture of membrane, intrahepatic cholestasis, hypothyroidism, fetal distress, postpartum hemorrhage, eclampsia and pregnancy-induced hypertension) across the three groups (Table 2). Three low birth weight infants (one in Group A and two in Group B) were seen. Three premature deliveries (one in Group A and two in Group 2) were observed.

Discussion

Maternal hyperviremia before delivery is a recognized risk factor for HBV immune failure and perinatal transmission. Up to 30% of immunization may fail if the pre-delivery HBV DNA level was higher than 10^8 copies/mL,^[13] and even the combined passive and active immunization is unable to completely block MTCT in patients with HBV DNA levels. Indeed, MTCT of HBV may occur in more than 15% of babies born to pregnant women with high viral load.^[14] Hence, it is of great importance to reduce the prenatal viral load in pregnant women in order to minimize the vertical HBV transmission.

Nucleos(t)ide analogs (NAs) have been shown to to reduce the viral loads during pregnancy and can effectively block the MTCT of HBV.^[9–12, 15–17] Oral antiviral drugs are usually given in the second and third trimesters of gestation. However, the exact timing of therapy is still controversial.^[13, 14, 18]

In our current study, we found that LdT can effectively reduce prenatal maternal hyperviremia regardless of it being given before pregnancy, at the second or third trimester. In mothers who received 28 weeks of LdT therapy either before pregnancy, or 24–28 weeks of gestation, or 28–32 weeks of gestation, no infant had HBV infection, demonstrating the great effectiveness of LdT in preventing MTCT.

Previous studies have shown that 12–17% of patients with postpartum flares may have HBeAg seroconversion.^[19] In our study, no severe flares (ALT > 5 × baseline value or 10 × upper limit of normal [ULN]) were found before delivery and after 28 weeks of gestation. No mothers in the LdT-treated group had severely increased serum CK(Creatine Kinase) levels during the entire course of treatment. No babies had serious defects at birth. This is consistent with the published studies that LdT did not cause infant birth defects.^[4, 15, 17, 18, 20]

In our study, we believe the reduced MTCT rate of HBV in infants could be attributed to the following reasons: **(a)** significantly reduced maternal viral load by LdT before delivery; and **(b)** timely administration of hepatitis B vaccine and hepatitis B immune globulin (within 2 hours of delivery).

Since the first 3 months are the critical time for fetal development, exposure to drugs at this time may carry a higher risk of deformity. Considering that antiviral treatment requires several weeks to effectively suppress serum viral loads,^[4] we propose that pregnant women in the immune-tolerant phase should take oral antiviral drugs at 28–32 weeks of gestation in order to effectively and safely block MTCT of HBV.

However, there are still shortcomings in our study. First, this is a retrospective study, so data and conclusions may be biased. Second, the sample size was relatively small. Third, there is a lack of long term follow up in the infants involved in this study. Further randomized, multi-center, long-term follow-up studies are needed to prove the reliability of our results.

Declarations

Ethics approval and consent to participate

All patients provided written informed consent and this study was approved by Ethics Committee of Xixi Hospital of Hangzhou. The data are anonymous, and the requirement for informed consent was therefore waived by Ethics Committee of Xixi Hospital of Hangzhou.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Liu S.R. participated in the topic selection and design of the thesis, Chen T.T. wrote the main manuscript text, Xiao Y.L. and Zhao C. sorted out the data, Chen X.X collected data. All authors reviewed the manuscript.

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References

1. European Association for the Study of the Liver. Electronic address eee and European Association for the Study of the L, EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol*, 2017, 67(2): 370–398. doi:10.1016/j.jhep.2017.03.021
2. Terrault NA, Bzowej NH, Chang K-M, et al, AASLD guidelines for treatment of chronic hepatitis B. *Hepatology (Baltimore, Md.)*, 2016, 63(1): 261–283. doi:10.1002/hep.28156
3. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. *The lancet. Gastroenterology & hepatology*, 2018, 3(6): 383–403. doi:10.1016/S2468-1253(18)30056-6
4. Han LF, Zheng JM, Zheng LQ, et al, Telbivudine can safely reduce mother-to-child transmission in chronic hepatitis B women after 12 weeks of gestation. *BMC Infect Dis*, 2019, 19(1): 614. doi:10.1186/s12879-019-4250-6
5. Pan CQ, Duan Z, Dai E, et al, Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load. *The New England journal of medicine*, 2016, 374(24): 2324–2334. doi:10.1056/NEJMoa1508660
6. Zhang L, Gui X, Wang B, et al, A study of immunoprophylaxis failure and risk factors of hepatitis B virus mother-to-infant transmission. *Eur J Pediatr*, 2014, 173(9): 1161–1168. doi:10.1007/s00431-014-2305-7
7. Zeng J, Zheng C and Li H, Effectiveness of tenofovir or telbivudine in preventing HBV vertical transmission for pregnancy. *Medicine (Baltimore)*, 2019, 98(14): e15092. doi:10.1097/md.00000000000015092

8. Hyun MH, Lee YS, Kim JH, et al, Systematic review with meta-analysis: the efficacy and safety of tenofovir to prevent mother-to-child transmission of hepatitis B virus. *Alimentary pharmacology & therapeutics*, 2017, 45(12): 1493–1505. doi:10.1111/apt.14068
9. 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(6): 1215–1221. doi:10.1016/j.jhep.2011.02.032
10. Han GR, Jiang HX, Yue X, et al, Efficacy and safety of telbivudine treatment: an open-label, prospective study in pregnant women for the prevention of perinatal transmission of hepatitis B virus infection. *J Viral Hepat*, 2015, 22(9): 754–762. doi:10.1111/jvh.12379
11. Sheng Q, Ding Y, Li B, et al, Efficacy and safety of nucleos(t)ide analogues to prevent hepatitis B virus mother-to-child transmission in pregnant women with high viremia: real life practice from China. *Int J Med Sci*, 2018, 15(8): 796–801. doi:10.7150/ijms.25047
12. Liu J, Wang J, Yan T, et al, Efficacy and safety of telbivudine and tenofovir disoproxil fumarate in preventing hepatitis B vertical transmission: A real-life practice. *J Viral Hepat*, 2019, 26(10): 1170–1177. doi:10.1111/jvh.13156
13. Liu Y, Wang M, Yao S, et al, Efficacy and safety of telbivudine in different trimesters of pregnancy with high viremia for interrupting perinatal transmission of hepatitis B virus. *Hepatol Res*, 2016, 46(3): E181-188. doi:10.1111/hepr.12525
14. 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(1): 51. doi:10.1186/s12876-017-0608-7
15. Song J, Yang F, Wang S, et al, Efficacy and safety of antiviral treatment on blocking the mother-to-child transmission of hepatitis B virus: A meta-analysis. *J Viral Hepat*, 2019, 26(3): 397–406. doi:10.1111/jvh.13036
16. He T, Bai Y, Cai H, et al, Safety and efficacy of lamivudine or telbivudine started in early pregnancy for mothers with active chronic hepatitis B. *Hepatology international*, 2018, 12(2): 118–125. doi:10.1007/s12072-017-9839-5
17. Li Z, Duan X, Hu Y, et al, Efficacy and Safety of Lamivudine or Telbivudine in Preventing Mother-to-Child Transmission of Hepatitis B Virus: A Real-World Study. *Biomed Res Int*, 2020, 2020: 1374276. doi:10.1155/2020/1374276
18. Han GR, Jiang HX, Wang CM, et al, Long-term safety and efficacy of telbivudine in infants born to mothers treated during the second or third trimesters of pregnancy. *J Viral Hepat*, 2017, 24(6): 514–521. doi:10.1111/jvh.12670
19. Pan CQ and Lee HM, Antiviral therapy for chronic hepatitis B in pregnancy. *Seminars in liver disease*, 2013, 33(2): 138–146. doi:10.1055/s-0033-1345718
20. Zeng H, Cai H, Wang Y, et al, Growth and development of children prenatally exposed to telbivudine administered for the treatment of chronic hepatitis B in their mothers. *Int J Infect Dis*, 2015, 33: 97–103. doi:10.1016/j.ijid.2014.09.002