systematic review

Efficacy of telbivudine on interruption of hepatitis B virus vertical transmission: a meta-analysis

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BACKGROUND AND OBJECTIVES: Hepatitis B virus (HBV) infection is one of the most common infections in the world. Vertical transmission is the main reason for the continued endemic infection rates, at least in Asia. This study aimed to investigate the efficacy of telbivudine on mother-to-child transmission (MTCT) interruption.
METHODS: Studies up to April 2012 were collected by searching Pubmed, EMBASE, the Cochrane Library, EBM Review, WangFang Database and China National Knowledge Infrastructure. Serum hepatitis B surface antigen (HBsAg) and HBV DNA in newborns and infants, maternal HBV DNA negative conversion and alanine transaminase (ALT) normalization and adverse events were analyzed.
RESULTS: Seven clinical trials involving 644 pregnant women were included in this meta-analysis. Telbivudine resulted in lower HBsAg and HBV DNA seroprevalence in newborns and infants. When maternal viral load prior to delivery was higher than 10^3 copies/mL, HBsAg or HBV DNA positivity had no statistical difference.
CONCLUSIONS: Telbivudine treatment has efficacy and safety on MTCT interruption during late pregnancy. In addition, we demonstrated benefit of telbivudine for mothers in terms of HBV DNA negative conversion and ALT normalization. Telbivudine treatment at the end of pregnancy should be considered in women with high viral load.

Hepatitis B is one of the most common infectious diseases in the world. Of the 2 billion individuals infected by HBV, over 350 million are chronically infected,[1] with chronic infection manifested by persistence of the virus and HBsAg in serum and production of viral antigens and HBV DNA in the liver. Cirrhosis, liver failure, or hepatocellular carcinoma (HCC) develop in 15% to 40% of individuals with chronic HBV infection,[2] which are responsible for 1 million deaths per year.[3] In southeast Asia, in the east or in Pacific regions, 30% to 50% of chronic infections in children are of vertical etiology linked to a high viral load in mothers. Presence of hepatitis B e antigen (HBeAg) in the mother's serum is associated with greater infectivity: The risk of perinatal HBV infection among infants born to HBV-infected mothers ranges from 10% to 40% in HBeAg-negative mothers to 70% to 90% in HBeAg-positive mothers.[4]

Although highly effective in preventing MTCT, standard passive-active immunoprophylaxis with hepatitis B immunoglobulin (HBIG) and the hepatitis B vaccine may have a failure rate as high as 10% to 15%.[5] History of threatened preterm labor, HBV in villous capillary endothelial cells, transplacental leakage of HBeAg-positive maternal blood, exposure to cervical secretions and maternal blood during labor and delivery, and specific allelic mutations in maternal HBV all may contribute to increased risk of MTCT.[6-8] Studies[7,9,10] show that the maternal HBV DNA level significantly affected the protective efficacy rate of passive-active immunoprophylaxis. The transition point in maternal viral load at which transmission rates begin to rise dramatically is approximately 10^6 to 10^8 copies/mL.[10-12] Thus, it might be an effective way to reduce the rate of HBV infection in infants by decreasing maternal HBV DNA level with antiviral therapy.

In women with high viral loads, antiviral treatment in the last trimester of pregnancy should be considered

to reduce the risk of in-utero transmission.[13,14] Five drugs are now FDA-approved for the treatment of HBV (interferon, lamivudine, adefovir, entecavir, and peginterferon alpha-2a) and divided into five categories (A, B, C, D, and X) for use in pregnancy. Currently there are no FDA category A anti-HBV medications. Lamivudine in category C (animal reproduction studies have shown an adverse effect on the fetus, there are no adequate and well-controlled studies in humans, and the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks) - it is safe and well tolerated in HIV-infected pregnancy[15-18] and may also provide additional protection in pregnant women with high-level viremia according to a meta-analysis.[19] Nevertheless, lamivudine resistant mutants emerge at a high rate of approximately 15% to 30% per year of therapy.[20] Even an HBV DNA mutation in a newborn due to lamivudine therapy during the last trimester of pregnancy in the mother has been reported.[21] Tenofovir in category B (animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women) was demonstrated a potent inhibitor of HIV and HBV replication, including activity against lamivudine-resistant HBV[22-27] and approved for CHB therapy by the US FDA in August 2008. Unfortunately, it has not been approved yet or is still undergoing phase III trials in many countries including China.

Telbivudine in category B has greater antiviral and clinical efficacy than lamivudine in patients with chronic hepatitis B, and less primary treatment failure and resistance.[28-33] Much less is known about the efficacy of telbivudine on preventing vertical transmission of HBV in pregnant patients. Recently, several studies[34-37] showed controversial results in blocking MTCT of telbivudine. This study aimed at meta-analyzing the published drug-based randomized and non-randomized controlled studies designed to evaluate the efficacy of telbivudine on the interruption of HBV MTCT in pregnant patients with high HBV DNA levels. According to the data, we evaluated the safety of telbivudine in mothers and infants additionally.

METHODS

Literature research and data extraction
We seached PubMed, EMBASE, the Cochrane Library, EBM Review, WangFang Database and China National Knowledge Infrastructure for relevant articles up to April 2012. The key words "telbivudine", "hepatitis B", "vertical transmission", "perinatal trans-

mission", "intrauterine transmission", "mother-to-child transmission", and their synonyms and related terms, were used. Reference lists from qualitative topic reviews and published clinical trials were also searched. Data extraction was conducted independently by two investigators (Liu MH and Liu JY). Articles were examined to eliminate duplicate reports of the same trials.

Inclusion and exclusion criteria
A inclusive clinical trial had to fulfil the following criteria: a prospective randomized controlled or non-randomized controlled study; telbivudine treatment for women infected by HBV in late pregnancy; maternal viral load higher than 10^6copies/mL at baseline; all infants given vaccine and HBIG within 12 hours of birth, vaccinated a second dose at weeks 4 and a final dose at week 24; serum parameters including HBsAg and HBV DNA as MTCT end-point. The most frequent reasons for exclusion were publication in an ineligible format including letters/abstracts or the results provided were not from original research including reviews/editorials; patients were co-infected with other hepatitis virus or human immunodeficiency virus; there was no control group; antiviral treatment began at the first or second trimester of gestation.

Efficacy measures
The primary end points of interruption of MTCT were indicated by serum HBsAg, HBeAg and HBV DNA of newborns or infants aged 6-12 months. Secondary end point was serum antibody to hepatitis B surface antigen (anti-HBs) of infants aged 6-12 months. The primary end point of maternal virological response and biochemical response were proportion of patients with undetectable HBV DNA and proportion of ALT nomalization, respectively.

Statistical methods
Outcomes were analyzed on an intention-to-treat basis. In this meta-analysis, the results were expressed as risk ratios (RRs) and 95% confidence intervals (CIs), and $P<.01$ was considered statistically significant. Heterogeneity between trials was evaluated by the Cochrane Q-test. In addition, the consistency of effects among trials was evaluated by I^2. A P value $<.10$ or $I^2>50\%$ was considered indicative of statistically significant heterogeneity. According to the absence of significant heterogeneity, we used a fixed-effect model to obtain quantitative, pooled, summary RRs. Publication bias was assessed by funnel plots which displayed the studies in a plot of effect size against sample size, which mapped the log standard error

against the log RR of individual studies.[38] Data analysis was conducted by using Review Manager software 5.0 (Cochrane Collaboration, Oxford, United Kingdom).

RESULTS

Search results and characteristics
We identified 72 articles by electronic search and excluded 54 irrelevant citations after reading abstracts. The process of article selection is shown in **Figure 1**. Among the 18 potentially relevant studies, two without control groups were excluded. One was rejected because patients in treatment group were treated with a combination of telbivudine and HBIG while patients in the control group were given HBIG alone. One was excluded because only one patient was enrolled. Six duplicate studies and one article without adequate information were excluded. Finally, seven clinical trials[36,37,39-43] involving 644 pregnant women

infected by HBV fulfilled our inclusion criteria. Of these, two were acquired from PubMed (Pan et al, 2012; Han et al, 2011), and the others were from Wang Fang Database and China National Knowledge Infrastructure published in Chinese (Chen et al, 2011; Yao et al, 2011; Cao et al, 2011; Zhang et al, 2010; Zhang et al, 2009). Only one of the included trials was a randomized, controlled clinical trial (Zhang et al, 2009). The 644 patients with a HBV DNA baseline level higher than 10^6 copies/mL had no historical antiviral-therapy before pregnancy except for ten in one study (Pan et al, 2012). Telbivudine was given to 350 patients in treatment group at an oral dose of 600 mg once daily mainly starting at 28 weeks gestational age in late pregnancy. The other 294 patients were left untreated and served as the controls. One patient received treatment from 12 weeks because of abnomal liver function (Zhang et al, 2009). The characteristics of the included studies were summarized in **Table 1, Table 2** and **Table 3**.

Table 1. Baseline characteristics of clinical trials.

First author, year	Study design	Age of mother	Group (n)	Interventions on mothers	Maternal HBV DNA level (lg copies/ml) (mean[SD])	
					Before intervention	Before delivery
Pan,[39] 2012	NRCT, P	20-40	arm1: 53	LDT 600mg od from week 12 to 30	8.08 (6.62-9.42)	2.68 (0.84)
		20-40	arm2: 35	no treatment	8.08 (6.67-9.08)	7.64 (0.72)
Han,[36] 2011	NRCT, P	20-40	arm1: 135	LDT 600mg od from week 20 to 32	8.10 (0.56)	2.44 (1.79)
		20-40	arm2: 94	no treatment	7.98 (0.61)	7.28 (0.66)
Chen,[40] 2011	NRCT, P	NA	arm1: 25	LDT 600mg od from week 28	>7.0	NA
		NA	arm2: 25	no treatment	>7.0	NA
Yao,[41] 2011	NRCT, P	28.9	arm1: 28	LDT 600mg od from week 28	7.5 (0.6)	3.3 (1.6)
			arm2: 30	no treatment	7.5 (0.7)	7.5 (0.6)
Cao,[42] 2011	NRCT, P	NA	arm1: 18	LDT 600mg od from week 28	7.78 (0.58)	3.87 (1.12)
		NA	arm2: 20	no treatment	7.45 (0.46)	7.42 (0.53)
Zhang,[43] 2010	NRCT, P	23-36	arm1: 60	LDT 600mg od from week 28	$lg[(6.62\pm0.9)\times10^6]$	$lg[(0.49\pm0.54)\times10^3]$
		24-37	arm2: 60	no treatment	$lg[(7.22\pm1.27)\times10^6]$	$lg[(7.46\pm1.06)\times10^6]$
Zhang,[37] 2009	RCT, P	NA	arm1: 31	LDT 600mg od from week 28	7.38 (0.81)	4.08 (0.52)
		NA	arm2: 30	no treatment	7.46 (0.45)	7.38 (0.57)

NRCT: non- randomized controlled trial ; RCT: randomized controlled trial P: prospective; LDT: telbivudine; od: once daily; NA: data not available; SD: Standard Error

Table 2. Outcomes of newborns/infants.

First author, year	Newborns within 24h			Infants aged 6-12 month			
	HBsAg +	HbeAg +	HBV DNA +	HBsAg +	HBeAg +	HBV DNA +	anti-HBs +
Pan, 2012	NA	NA	NA	0/54	0/54	0/54	NA
	NA	NA	NA	3/35	3/35	3/35	NA
Han, 2011	13/136	NA	NA	0/132	NA	0/132	132/132
	28/94	NA	NA	7/88	NA	7/88	81/88
Chen, 2011	1/25	NA	0/25	0/25	NA	0/25	NA
	5/25	NA	4/25	4/25	NA	4/25	NA
Yao, 2011	1/28	NA	NA	0/28	NA	NA	NA
	5/30	NA	NA	4/30	NA	NA	NA
Cao, 2011	3/18	NA	0/18	NA	NA	NA	NA
	2/20	NA	1/20	NA	NA	NA	NA
Zhang, 2010	6/60	NA	5/60	1/60	NA	1/60	NA
	18/60	NA	18/60	11/60	NA	11/60	NA
Zhang, 2009	2/31	NA	NA	0/31	NA	NA	NA
	2/30	NA	NA	4/30	NA	NA	NA

NA: data not available.

Table 3. Outcomes of mothers and adverse events.

First author, year	ALT normalization before delivery	Maternal HBV DNA (-) before delivery	Adverse events	
			Mothers	Infants
Pan, 2012	46/53	1/53	0/53	3/54
	21/35	0/53	0/35	1/35
Han, 2011	30/36	NA	12/135	0/136
	21/37	NA	5/94	0/94
Chen, 2011	NA	NA	0/25	0/25
	NA	NA	0/25	0/25
Yao, 2011	NA	NA	3/20	0/20
	NA	NA	2/30	0/30
Cao, 2011	NA	1/18	NA	0/18
	NA	0/20	NA	0/20
Zhang, 2010	NA	52/60	13/60	0/60
	NA	0/60	0/60	0/60
Zhang, 2009	NA	NA	0/31	8/31
	NA	NA	0/30	9/30

(-): HBV DNA undetectable; NA: data not available.
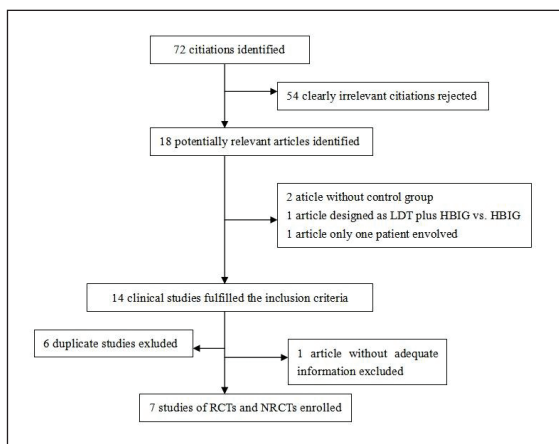
Figure 1. Flow chart of literature selection. LDT: telbivudine, HBIG: hepatitis B immunoglobulin, RCT: randomized controlled trial, NRCT: non- randomized controlled trial.

Figure 2. HBsAg and HBV DNA seroprevalence in newborns.

Figure 3. HBsAg and HBV DNA seroprevalence in infants.
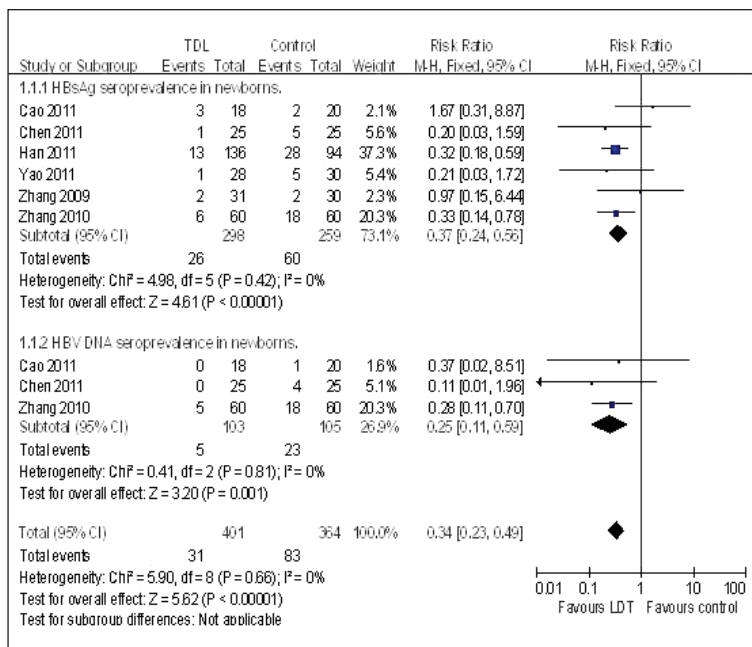
Serum HBsAg and HBV DNA of newborns within 24h after birth

The efficacy of telbivudine on blocking MTCT in newborns was assessed in six trials containing the data of HBsAg seroprevalence and evaluated in three trials providing HBV DNA seroprevalence. Analysis showed efficacy of telbivudine on interrupting vertical transmission. A fixed-effect model was used because of the absence of heterogeneity (chi-square=4.98, P=0.42, I^2=0%). The overall estimate for RR of telbivudine group vs. control group was 0.37 [95% CI 0.24, 0.56] (P<.00001) in serum HBsAg positivity (**Figure 2**). It was 0.25 [95% CI 0.11, 0.59] (P=0.001) in serum HBV DNA positivity, heterogeneity analysis chi-square=0.41, P=0.81, I^2=0% (**Figure 2**).
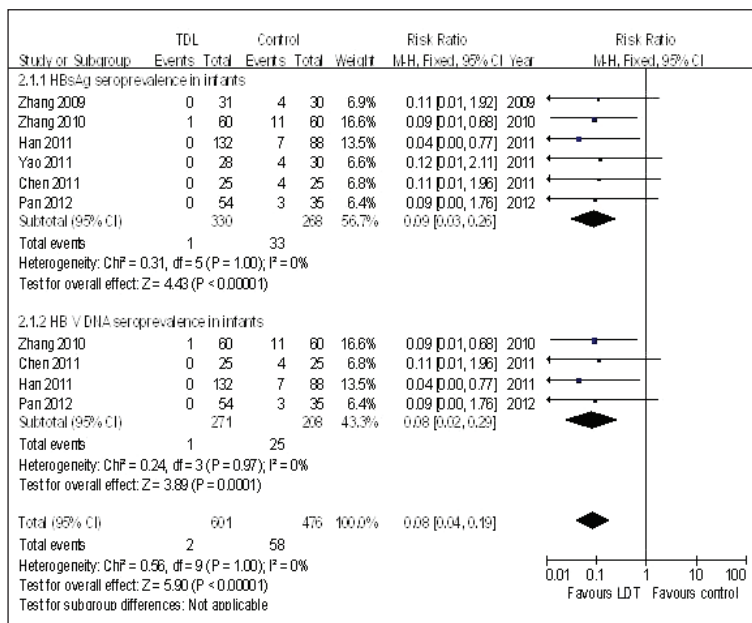
Serum HBsAg and HBV DNA of infants aged 6-12 months

Six trials providing data of serum HBsAg positivity in infants were evaluated. We observed a significant reduce of HBsAg seroprevalence in the treatment groups. The summary RR was 0.09 [95% CI 0.03, 0.26] (P<.00001) (**Figure 3**). Q-test for heterogeneity chi-square=0.31, P=1.00, I^2=0%. Only 4 trials compared serum HBV DNA positivity in infants. All these trials showed a significant effect among infants from treated group with a common RR of 0.08 [95% CI 0.02, 0.29] (P=.0001) in favor of treatment (**Figure 3**). Q-test for heterogeneity chi-square=0.24, P=0.97, I^2=0%.

Maternal HBV DNA negative conversion and alanine transaminase normalization

Only three trials contained data of maternal HBV DNA negative conversion and two had data of ALT normalization prior to delivery. In comparison with no treatment, telbivudine therapy resulted in higher HBV DNA negative conversion rate and ALT normalization rate among mothers. The pooled RR was 37.68 [95% CI 7.45, 190.47] (P<.0001), and 1.46 [95% CI 1.18, 1.80] (P=.0006), respectively (**Figure 4**).
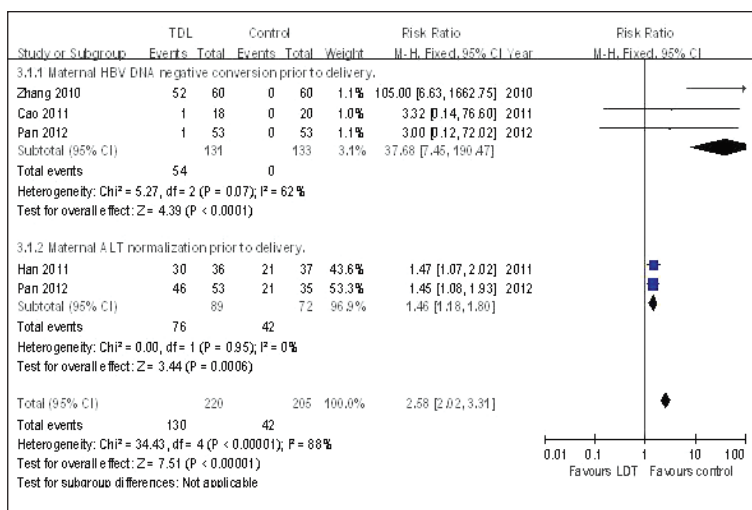
Figure 4. Maternal HBV DNA negative conversion and ALT normalization prior to delivery.
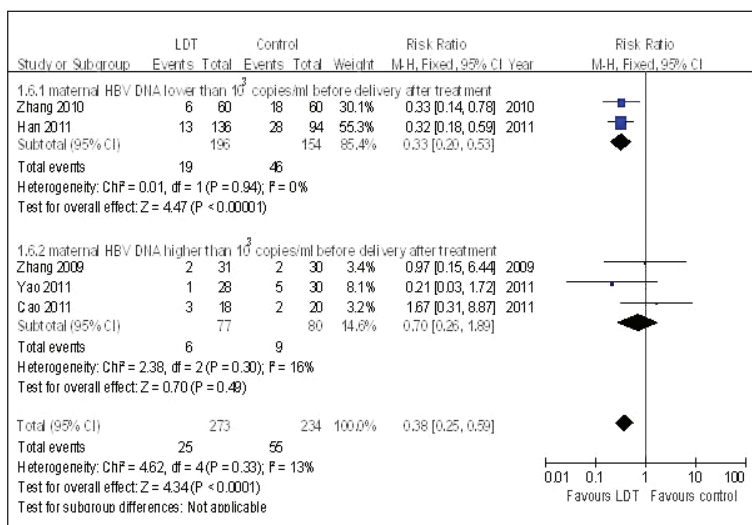
Figure 5. Influence of maternal HBV DNA level prior to delivery on HBsAg seroprevalence among newborns.

Serum HBsAg of newborns and infants born to mothers with different viral loads

To investgate the influence of maternal HBV DNA levels on vertical transmission, we made an analysis by dividing the studies into two subgroups according to maternal HBV DNA levels before delivery in treated groups. When maternal HBV DNA level was lower than 10^3 copies/mL after treatment, HBsAg seroprevalence in newborns was reduced in comparison to the control group. The summary RR was 0.33 [95% CI 0.20, 0.53] (*P*<.00001) (**Figure 5**). However, when maternal HBV DNA level was higher than 10^3 copies/

mL, HBsAg positivity in the two groups had no statistical difference [RR 0.7; 95% CI 0.26, 1.89] (*P*=.49) (**Figure 5**).

Among infants born to mothers with a HBV DNA level lower than 10^3copies/mL, the RR of HBsAg prevalence was 0.07 [95% CI 0.02, 0.31] (*P*=.0003) (**Figure 6**). No statistical difference was observed in HBsAg prevalence of infants when mothers' HBV DNA level was higher than 103copies/mL [RR 0.11; 95% CI 0.01, 0.87] (*P*=.04) (**Figure 6**). These demonstrated that high maternal viral loads prior to delivery after treatment implied small efficacy of telbivudine on blocking vertical transmission of HBV and also corresponded to the theory regarding high maternal viral load as a high risk of MTCT.

Safety

Three studies reported adverse events in mothers (Han et al, 2011; Yao et al, 2011; Zhang et al, 2010), two of which described adverse events as serum creatine kinase (CK) elevation (Yao et al, 2011; Zhang et al, 2010) and the other one considered the events dug-unrelated (Han et al, 2011). Two studies reported adverse events among infants. One reported serum CK elevation (Zhang et al., 2009). In the other one, pneumonia occurred in three infants from the treated group and one from the control group, but it was not clear whether the occurrence was drug-related (Pan et al, 2012). Incidence of adverse events among mothers had a significant difference with a Peto odds ratio of 3.35 [95% CI 1.66, 6.73] (*P*=.0007). Adverse events among newborns/infants did not differ significantly between telbivudine and untreated groups [Peto odds ratio 0.98; 95% CI 0.37, 2.61](*P*=.97).

DISCUSSION

Multiple clinical trials have confirmed that telbivudine showed significantly greater HBV DNA suppression with less primary treatment failure and resistance in general in patients with chronic hepatitis B. Telbivudine has been generally well tolerated, with a low adverse effect profile.[44] Telbivudine treatment at the end of pregnancy should be considered in women with a very high viral load to diminish the risk of vertical transmission. However, it is still controversial because of lack of data and evidence of efficacy. This meta-analysis adds further support to the efficacy of telbivudine on interrupting MTCT.

Our study showed significant efficacy of telbivudine on preventing vertical transmission indicated both by serum HBsAg and HBV DNA in newborns (RR was 0.37 and 0.09, respectively.) or infants (RR was 0.25 and 0.08, respectively.). Transmission rate indicated by

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serum HBsAg in telbivudine group was much lower than that in control group among infants (0.3%, 1/330 vs. 12.3%, 33/268). Similarly, it was 0.4% (1/271) and 12.0% (25/208) respectively indicated by serum HBV DNA. It was demonstrated that MTCT incidence would increase in newborns or infants if maternal HBV DNA level was higher than 10^3 copies/mL prior to delivery. Analysis of HBV DNA negative conversion and ALT normalization also confirmed the definite efficacy of telbivudine on mothers.

Serum HBsAg, HBeAg, and HBV DNA in newborns or infants are frequently used as routine indicators of MTCT. Beasley et al[45] recommended high titers of HBsAg within 24 hours after birth and becoming HBsAg carrier after passive-active immunoprophylaxis as two criteria for perinatal infection diagnosis. Thus, evaluating MTCT within 24 hours after birth seems not entirely reasonable because the efficacy of the serovaccination must be confirmed in all children by a serologic examination (HBsAg and anti-HBs) at some time after the last vaccination.[46] Though detecting techniques for serum HBV DNA now available are much more sensitive than which for HBV markers,[9,47] HBV DNA is probably undetectable in patient infected by HBV, especially HBV carriers. So HBV DNA used as indicator solely to estimate vertical transmission rate would lead an unreliable result. Therefore, combination of HBsAg and HBV DNA testing within 24 hours and 6 to 12 months after birth should be suggested.

There are reports of symptomatic myopathy, peripheral neuropathy and cardiac arrhythmia in patients receiving telbivudine, as well as a significantly higher incidence of grade 3 to 4 serum CK elevations noted in telbivudine-treated compared to lamivudine-treated patients at 2 years (12.9% versus 4.1%).[30,48,49] CK elevation was observed in three analyzed studies and normalization occurred after drug discontinuance. Other adverse events or birth defects were not recorded. The difference of adverse events among infants between treated and control groups was not significant. Additionally, hepatitis flares can occur after discontinuation of antiviral therapy.[50] There are few data about excretion of telbivudine into breast milk. For these reasons, close monitoring is necessary if patients are to receive telbivudine treatment
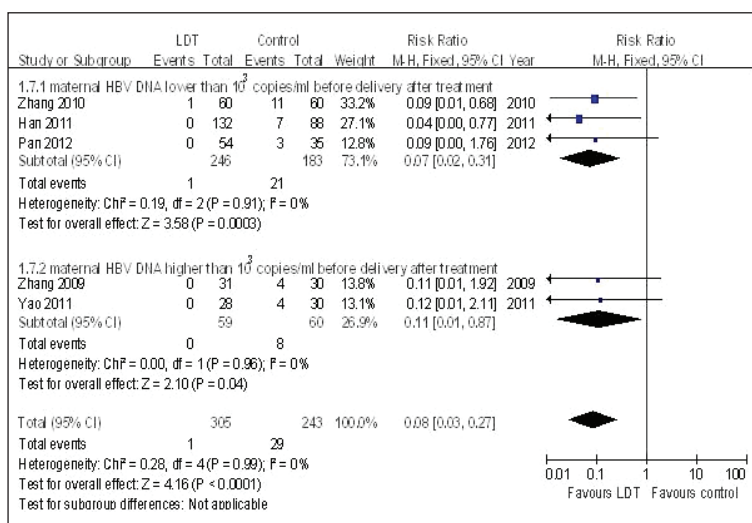

Figure 6. Influence of maternal HBV DNA level prior to delivery on HBsAg seroprevalence in infants.

during pregnancy. The 6-week postpartum visit should serve as an opportunity to establish referrals.[51]

This meta-analysis presents some potential limitations. Firstly, the majority of studies included were non-randomized controlled trials and the only randomized one had not described the method used to generate the allocation sequence. It was difficult to blind and allocate subjects randomly in consideration of informed consent before telbivudine therapy. Secondly, few studies and small samples were included in this meta-analysis. Thirdly, lack of some important information such as maternal HBeAg status and data of long-term postpartum follow up make it impossible to analyse further. Finally, publication bias existed in our study. Compared to positive studies, negative studies may be less likely to be published or more likely to take longer to be published, which can affect the validity of meta-analysis.[52]

In conclusion, telbivudine has a clear efficacy and safety on interrupting perinatal transmission of HBV in pregnant women with high viral load. It is also associated with a significantly greater proportion of patients achieving HBV DNA negative conversion and ALT normalization. Moreover, the efficacy of telbivudine on blocking MTCT can be implied by maternal HBV DNA level prior to delivery after treatment.

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