

A meta-analysis of lamivudine for interruption of mother-to-child transmission of hepatitis B virus

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Abstract

AIM: To determine the therapeutic effect of lamivudine in late pregnancy for the interruption of mother-to-child transmission (MTCT) of hepatitis B virus (HBV).

METHODS: Studies were identified by searching available databases up to January 2011. Inclusive criteria were HBV-carrier mothers who had been involved in randomized controlled clinical trials (RCTs) with lamivudine treatment in late pregnancy, and newborns or infants whose serum hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg) or HBV DNA had been documented. The relative risks (RRs) for interruption of MTCT as indicated by HBsAg, HBV DNA or HBeAg of newborns or infants were calculated with 95% confidence interval (CI) to estimate the efficacy of lamivudine treatment.

RESULTS: Fifteen RCTs including 1693 HBV-carrier

mothers were included in this meta-analysis. The overall RR was 0.43 (95% CI, 0.25-0.76; 8 RCTs; $P_{\text{heterogeneity}} = 0.04$) and 0.33 (95% CI, 0.23-0.47; 6 RCTs; $P_{\text{heterogeneity}} = 0.93$) indicated by newborn HBsAg or HBV DNA. The RR was 0.33 (95% CI, 0.21-0.50; 6 RCTs; $P_{\text{heterogeneity}} = 0.46$) and 0.32 (95% CI, 0.20-0.50; 4 RCTs; $P_{\text{heterogeneity}} = 0.33$) indicated by serum HBsAg or HBV DNA of infants 6-12 mo after birth. The RR (lamivudine *vs* hepatitis B immunoglobulin) was 0.27 (95% CI, 0.16-0.46; 5 RCTs; $P_{\text{heterogeneity}} = 0.94$) and 0.24 (95% CI, 0.07-0.79; 3 RCTs; $P_{\text{heterogeneity}} = 0.60$) indicated by newborn HBsAg or HBV DNA, respectively. In the mothers with viral load $< 10^6$ copies/mL after lamivudine treatment, the efficacy (RR, 95% CI) was 0.33, 0.21-0.53 (5 RCTs; $P_{\text{heterogeneity}} = 0.82$) for the interruption of MTCT, however, this value was not significant if maternal viral load was $> 10^6$ copies/mL after lamivudine treatment ($P = 0.45$, 2 RCTs), as indicated by newborn serum HBsAg. The RR (lamivudine initiated from 28 wk of gestation *vs* control) was 0.34 (95% CI, 0.22-0.52; 7 RCTs; $P_{\text{heterogeneity}} = 0.92$) and 0.33 (95% CI, 0.22-0.50; 5 RCTs; $P_{\text{heterogeneity}} = 0.86$) indicated by newborn HBsAg or HBV DNA. The incidence of adverse effects of lamivudine was not higher in the mothers than in controls ($P = 0.97$). Only one study reported side effects of lamivudine in newborns.

CONCLUSION: Lamivudine treatment in HBV carrier-mothers from 28 wk of gestation may interrupt MTCT of HBV efficiently. Lamivudine is safe and more efficient than hepatitis B immunoglobulin in interrupting MTCT. HBV MTCT might be interrupted efficiently if maternal viral load is reduced to $< 10^6$ copies/mL by lamivudine treatment.

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Key words: Hepatitis B virus; Lamivudine; Mother-to-child transmission; Efficacy; Meta-analysis

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INTRODUCTION

Hepatitis B virus (HBV) infection is a global issue of public health. More than 350 million people suffer from chronic HBV infection, the commonest cause of hepatocellular carcinoma^[1]. Mother-to-child transmission (MTCT) of HBV, the commonest mode of transmission worldwide, may occur either in utero or perinatally. In East and Southeast Asia, in utero transmission of HBV is rare, whereas perinatal transmission is common. MTCT of HBV is associated with a very high rate of chronicity, especially in countries where HBV is endemic. This is attributed to the high rate of hepatitis B e antigen (HBeAg)-positive infection in women of child-bearing age in these areas and the efficient transmission of HBV from mothers to their newborns^[2-4]. Therefore, prevention of MTCT is the most important strategy in the eradication of HBV infection.

Joint immunoprophylaxis with hepatitis B immunoglobulin (HBIG) and three doses of hepatitis B vaccines to infants born to hepatitis B surface antigen (HBsAg)-positive mothers are known to be safe and effective. However, 5%-10% of infants of HBV-positive mothers become infected even with proper vaccination^[5]. Very high maternal viremia, in utero infection, or escape mutants are possible reasons for vaccination failure, while immunocompromised hosts also risk vaccination failure^[6]. Of those, maternal high viral load and HBeAg positivity contribute greatly to MTCT despite the use of passive-active immunoprophylaxis in newborns. A meta-analysis of individual patient data of the three randomized trials indicated that the passive-active immunoprophylaxis had 100% protective efficacy if maternal serum HBV DNA was lower than 150 pg/mL compared with 68% if maternal serum HBV DNA was higher than 150 pg/mL^[7]. The recommended dose of HBIG may be insufficient to neutralize the huge virus load that the infants are exposed to at the time of birth in cases whose mothers have very high serum HBV DNA levels^[8]. In addition, immunized children born to genotype C HBV-infected mothers may have a higher rate of breakthrough infection than those born to genotype B-infected mothers in Southeast Asia^[9]. Thus, administration of antiviral therapy to lower the maternal serum HBV DNA levels may reduce the rate of perinatal infection in newborns born to mothers who have high serum HBV DNA levels or who are infected with HBV genotype C, the major HBV

genotype endemic in mainland China^[10].

The antiviral drug with a record of safe use in pregnant women is lamivudine^[11]. In HBeAg-positive mothers who had serum HBV DNA > 10⁹ copies/mL, lamivudine treatment started between weeks 34 and 38 of pregnancy until delivery might greatly decrease the perinatal infection of their newborns who routinely received the combined immunoprophylaxis, as compared with historical controls^[12]. However, some studies have demonstrated that treatment with lamivudine or HBIG did not reduce the perinatal infection rate significantly among women with an extremely high HBV DNA load, and among those with reduced maternal HBV DNA, even with undetectable status, this treatment could not guarantee exemption of their newborns' HBV infection in late pregnancy^[13,14]. These controversial results necessitate meta-analyses by pooling data of the available studies to address the following questions^[8]. (1) At which maternal serum HBV DNA level does the antiviral therapy have a clear beneficial effect? (2) How early in pregnancy should antiviral therapy be initiated? (3) Is lamivudine safe in pregnancy or in nursing mothers? A recent meta-analysis of randomized controlled trials (RCTs) using the data up to October 2009 has demonstrated that lamivudine treatment in HBV-infected mothers with a high degree of infectiousness in late pregnancy effectively prevented MTCT^[15]. However, the first two questions have not been fully answered. In this study, we performed a meta-analysis of the randomized, placebo controlled trials up to January 2011, evaluated the efficacy of lamivudine in late pregnancy as compared with placebo or control in interruption of MTCT of HBV and determined the maternal HBV DNA level that lamivudine treatment has a clear beneficial effect. We also investigated the safety of lamivudine treatment in mothers and their newborns in an attempt to provide useful data for interrupting MTCT of HBV.

MATERIALS AND METHODS

Search strategy and selection criteria

We searched MEDLINE, EMBASE, the Cochrane controlled trials register, the Cochrane Library, and China Biological Medicine Database for publications (including abstracts) in English or Chinese, up to January 2011. The keywords used for searching were "MTCT (vertical transmission, perinatal transmission or intrauterine transmission)" and "hepatitis B virus (HBV or hepatitis B)" and "antiviral treatment (lamivudine)". We also did a full manual search from bibliographies of selected studies to identify additional studies. We contacted some of the authors to collect further information.

The following studies were included: RCTs; lamivudine treatment for HBV-carrier mothers in late pregnancy; passive-active immunoprophylaxis for newborns after birth; MTCT; MTCT diagnosed based on the serum parameters including HBsAg, HBeAg and HBV DNA; and relative risks (RRs) with the 95% confidence intervals (CIs). The following studies were excluded: unclear his-

tory of the immunoprophylaxis of newborns or infants; the patients co-infected with hepatitis C or hepatitis D virus or human immunodeficiency virus; participants who had received antiviral treatment before pregnancy or without control subjects. We only included the most recent studies or studies with a larger number of participants when more than one studies were published by the same authors.

Data extraction

Data were independently extracted by two investigators (Han L and Zhang HW) and checked by the other authors. The concordance rate between the two investigators was more than 90%. Discrepancies were resolved by consensus. The following information was extracted using a standardized form: the details of the study (study design, citation, publication date); the characteristics of the subjects (number of included mothers, maternal serum HBV HBsAg and HBeAg); the interventions on mothers (lamivudine treatment and comparative treatment regimen used for each arm, dosage, and duration) and the outcomes (serum HBsAg, HBeAg and HBV DNA of newborns within 24 h and infants within 6-12 mo after birth) and adverse events.

Quality assessment

Two investigators (Han L and Zhang HW) independently rated the quality of each retrieved study. Disagreement was resolved by discussion among the investigators. Trials of high quality (with low risk of bias) should fulfil two or three of the following elements: adequate generation of the allocation sequence, adequate allocation concealment, and adequate blindness. Trials of low quality (with high risk of bias) were those having one or none of these elements^[16,17].

Statistical analysis

Freeware program Review Manager (Version 5.0 for Windows, Cochrane Collaboration, Oxford, United Kingdom, 2010) was applied to conduct statistical analysis. The effect measures of interest were RRs and the corresponding 95% CIs. Statistical heterogeneity among studies was evaluated using χ^2 test, *P* values, and *I*² statistics^[18]. Statistical heterogeneity was defined as *P* < 0.10 or *I*² > 50%. A random-effect model was used to obtain summary RRs. The random-effect model adjusted for variability of results among trials provided a more conservative estimate of an effect using wider CI^[19]. Publication bias was evaluated using 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^[20]. All statistical tests were two-sided.

RESULTS

We identified 106 citations from the literature. The relevant trials are shown in Figure 1. Eighteen irrelevant ci-

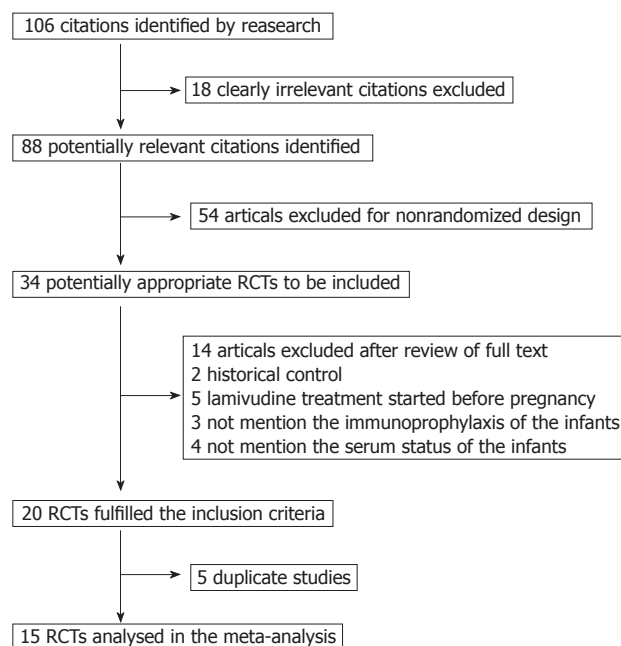


Figure 1 Flow chart of study recruitment. RCTs: Randomized controlled clinical trials.

tations were excluded after abstract preview. Among the remaining 88 articles, 54 were excluded because of non-randomized design after the full text review. Of the remaining 34 potentially appropriate RCTs, 2 were excluded because of historical controls, 5 were excluded because the lamivudine treatment started before pregnancy, 3 were excluded for not having detailed information on the immunoprophylaxis of newborns, and 4 were excluded because the serum HBV parameters of the infants were not mentioned. After removing the 5 duplicate studies, a total of 15 RCTs were included eventually^[21-35]. Of the 15 RCTs, 2 were from PubMed^[25,35], 12 from China Biological Medicine Database published in Chinese^[21-24,27-34], and 1 from reference lists^[26]. Of those, 10 investigated MTCT by measuring the newborn's blood within 24 h after birth^[21-23,25,26,28-30,34-35], 11 investigated MTCT by measuring the infant's sera 6-12 mo after birth^[21-25,27-28,30-33], 11 measured maternal HBV DNA levels when they were enrolled in the trials before lamivudine treatment^[21,23,25-27,29-31,33-35], 10 measured maternal HBV DNA levels after treatment before delivery^[21,25-27,29-31,33-35]. The regimen of lamivudine treatment varied and some RCTs had several intervention groups such as HBIG or lamivudine plus HBIG groups. Three articles reported adverse events in mothers with lamivudine treatment^[25,26,34], only one article reported adverse events in the infant whose mother received lamivudine treatment^[25]. A total of 1693 HBV-carrier mothers were included. The characteristics of the included studies are summarized in Table 1. Of the 15 trials, 6 adequately described the generation of the allocation sequence^[26-29,34,35], 2 concealed treatment allocation and double blinded methods were described^[25,26]. The remaining trials did not report the methodological quality.

Table 1 General information of included randomized controlled trials

First author, year ^[Ref.]	Group (n)	Interventions on mothers	Maternal HBV DNA level ¹		Newborns within 24 h			Infants within 6-12 mo			Adverse events	
			Before intervention	Before delivery	HBsAg (+)	HBeAg (+)	HBV DNA (+)	HBsAg (+)	HBeAg (+)	HBV DNA (+)	Mothers	Infants
Zhang, 2010 ^[21]	Arm 1:50	3TC 100 mg od from week 28	6.83 ± 0.90	3.65 ± 0.54	6/50	-	5/50	1/50	-	1/50	0	0
	Arm 2:50	No treatment	6.87 ± 1.67	6.88 ± 1.08	17/50	-	18/50	8/50	-	8/50	-	-
Han, 2010 ^[22]	Arm 1:52	3TC 100 mg od from week 20	-	-	5/52	-	1/52	0/42	-	0/42	0	0
	Arm 2:61	200 IU HBIG every 2 wk from week 28	-	-	26/61	-	7/61	9/55	-	9/55	0	0
Han, 2009 ^[23]	Arm 1:57	3TC 100 mg od from week 20	7.5 ± 0.50	-	6/57	-	1/57	0/46	-	0/46	0	0
	Arm 2:66	200 IU HBIG every 2 wk from week 28	7.5 ± 0.72	-	27/66	-	8/66	10/59	-	10/59	0	1/66
Su, 2009 ^[24]	Arm 1:128	3TC 100 mg od from week 32, 200 IU HBIG at week 28, 32, 36	-	-	-	-	-	6/128	-	-	0	0
	Arm 2:120	200 IU HBIG at week 28, 32, 36	-	-	-	-	-	17/120	-	-	-	-
Xu, 2009 ^[25]	Arm 1:63	3TC 100 mg od from week 32	9.35 ± 0.21	7.71 ± 1.49	17/56	-	7/56	10/56	-	11/56	7/89	10/56
	Arm 2:62	Placebo	9.43 ± 0.21	9.34 ± 0.22	14/59	-	24/59	23/59	-	27/59	6/61	12/59
Shi, 2009 ^[26]	Arm 1:49	3TC 100 mg od from week 28	7.24 ± 1.90	4.49 ± 3.25	3/49	-	1/49	-	-	-	2/51	-
	Arm 2:116	100 IU HBIG at week 28, 32, 36	6.31 ± 2.13	5.86 ± 2.62	8/116	-	4/116	-	-	-	3/146	-
	Arm 3:43	Placebo	6.40 ± 2.12	6.19 ± 2.57	10/43	-	5/43	-	-	-	2/84	-
Yang, 2008 ^[27]	Arm 1:45	3TC 100 mg od from week 24	6.99 ± 0.84	5.10 ± 0.80	-	-	-	1/45	-	-	-	0
	Arm 2:42	100 IU HBIG at week 28, 32, 36	6.87 ± 0.92	6.87 ± 0.92	-	-	-	6/42	-	-	-	0
Guo, 2008 ^[28]	Arm 1:70	3TC 100 mg od from week 28	-	-	6/70	-	8/70	4/70	-	6/70	-	-
	Arm 1:40	No treatment	-	-	10/40	-	13/40	12/40	-	18/40	-	-
Xiang, 2007 ^[29]	Arm 1:21	3TC 100 mg od from week 28	8.02 ± 1.15	4.58 ± 1.22	1/21	3/21	-	-	-	-	-	-
	Arm 2:25	200 IU HBIG every month from month 4	7.63 ± 1.23	5.12 ± 1.07	2/25	2/25	-	-	-	-	-	-
	Arm 3:18	No treatment	7.16 ± 0.79	6.88 ± 1.36	5/18	3/18	-	-	-	-	-	-
Feng, 2007 ^[30]	Arm 1:48	3TC 100 mg od from week 28	8.34 ± 1.23	4.85 ± 1.27	8/48	-	9/48	7/48	-	7/48	0	0
	Arm 1:42	No treatment	8.26 ± 1.87	8.56 ± 1.08	17/42	-	19/42	16/42	-	16/42	0	0
Li, 2006 ^[31]	Arm 1:36	3TC 100 mg od from week 24	6.89 ± 0.82	5.08 ± 0.76	-	-	-	1/36	-	-	0	0
	Arm 2:44	No treatment	> 5.00	> 5.00	-	-	-	7/44	-	-	0	0
Li, 2006 ^[32]	Arm 1:40	3TC 100 mg od from week 28 and 200 IU HBIG at week 28, 32, 36	-	-	-	-	-	1/35	1/35	1/35	0	0
	Arm 2:37	200 IU HBIG at week 28, 32, 36	-	-	-	-	-	7/32	6/32	6/32	0	0
Han, 2005 ^[33]	Arm 1:43	3TC 100 mg od from week 28	7.15 ± 0.91	5.43 ± 0.85	-	-	-	0/43	-	0/43	0	0
	Arm 1:35	No treatment	> 5.60	> 5.60	-	-	-	5/35	-	-	0	0
Shi, 2005 ^[34]	Arm 1:21	3TC 100 mg od from week 28	8.72 ± 0.69	6.59 ± 1.06	1/21	3/21	2/21	-	-	-	1/21	0
	Arm 1:18	No treatment	8.93 ± 1.12	9.05 ± 0.26	1/18	2/18	8/18	-	-	-	0	0
Li, 2003 ^[35]	Arm 1:56	200 IU HBIG every 4 wk from week 28	7.38 ± 1.17	5.28 ± 2.77	3/56	7/56	-	-	-	-	0	0
	Arm 2:43	3TC 100 mg od from week 28	7.49 ± 0.54	5.33 ± 1.34	1/43	7/43	-	-	-	-	0	0
	Arm 3:52	No treatment	7.05 ± 1.29	6.23 ± 3.66	8/52	11/52	-	-	-	-	0	0

3TC: Lamivudine; HBIG: Hepatitis B immunoglobulin; IU: International unit; mg: Milligram; od: Once daily; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; -: Data not available. ¹Log₁₀ HBV DNA (mean ± SD).

Table 2 Methodological quality of included randomized clinical trials

First author, year ^[Ref.]	Generation of allocation sequence	Allocation concealment	Blinding	Methodological quality
Han, 2010 ^[22]	Unclear	Unclear	Unclear	Low
Zhang, 2010 ^[21]	Unclear	Unclear	Unclear	Low
Han, 2009 ^[23]	Unclear	Unclear	Unclear	Low
Su, 2009 ^[24]	Unclear	Unclear	Unclear	Low
Xu, 2009 ^[25]	Unclear	Adequate	Adequate	High
Shi, 2009 ^[26]	Adequate	Adequate	Adequate	High
Yang, 2008 ^[27]	Adequate	Unclear	Unclear	Low
Guo, 2008 ^[28]	Adequate	Unclear	Unclear	Low
Xiang, 2007 ^[29]	Adequate	Unclear	Unclear	Low
Feng, 2007 ^[30]	Not done	Not done	Not done	Low
Li, 2006 ^[31]	Not done	Not done	Not done	Low
Li, 2006 ^[32]	Not done	Not done	Not done	Low
Han, 2005 ^[33]	Not done	Not done	Not done	Low
Shi, 2005 ^[34]	Adequate	Unclear	Unclear	Low
Li, 2003 ^[35]	Adequate	Unclear	Unclear	Low

As a result, 2 trials were classified as of high quality and the remaining 13 trials were of low quality (Table 2).

Effects of lamivudine on interruption of MTCT indicated by serum HBsAg, HBeAg or HBV DNA of newborns within 24 h after birth

Compared with controls (placebo or no treatment), lamivudine treatment for the HBV-carrier mothers significantly interrupted MTCT. The efficacy (RR, 95% CI) of lamivudine treatment *vs* control in 8 RCTs was 0.43, 0.25-0.76; $P < 0.01$, with significant heterogeneity ($P = 0.04$, $I^2 = 52\%$) as indicated by serum HBsAg (Figure 2A). It was 0.33, 0.23-0.47 in 6 RCTs; $P < 0.01$, with minimum heterogeneity ($P = 0.93$, $I^2 = 0$) indicated by serum HBV DNA (Figure 2B). However, the corresponding values shown by HBeAg was not significant in 3 RCTs (0.86, 0.43-1.69; $P = 0.65$) with minimum heterogeneity ($P = 0.87$, $I^2 = 0$) (Figure 2C). The funnel

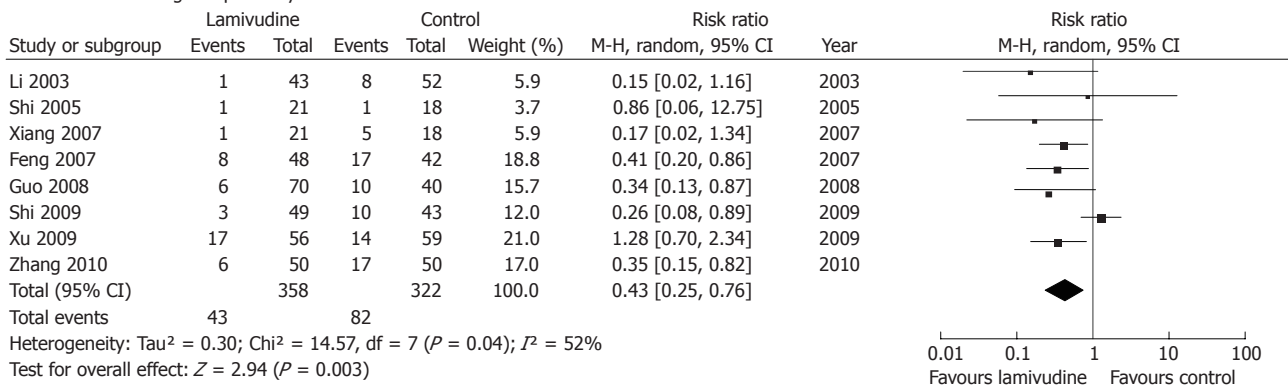
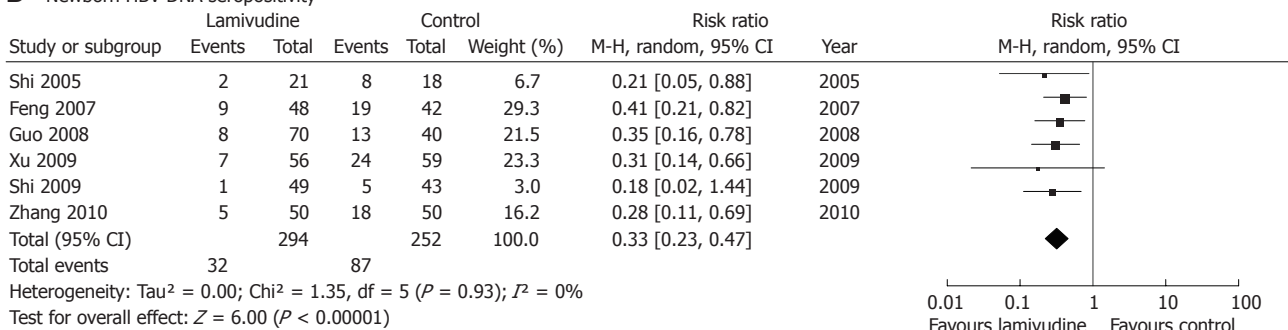
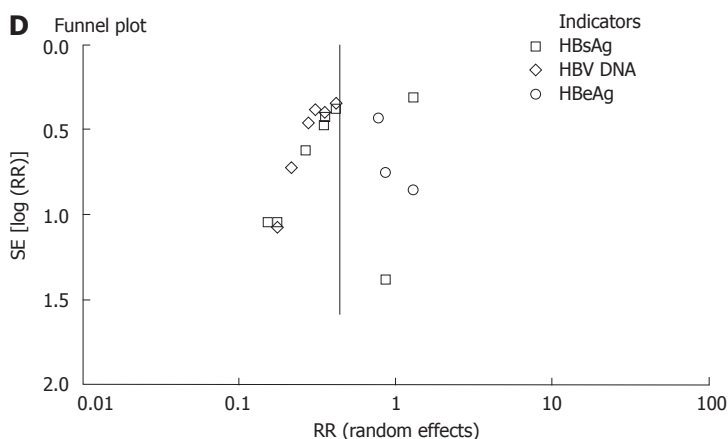
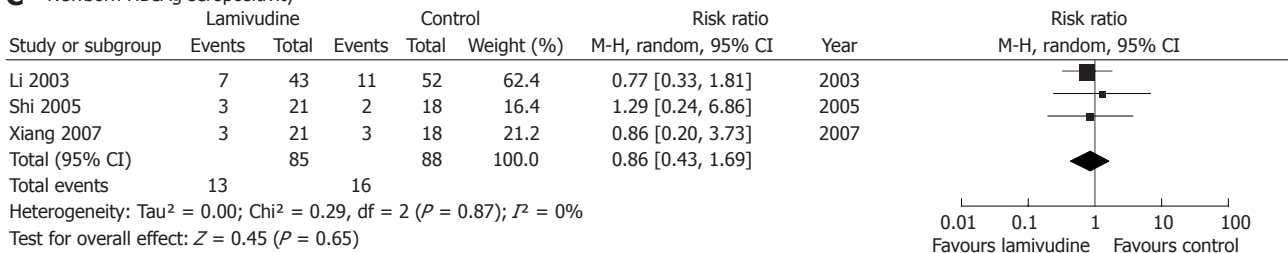
A Newborn HBsAg seropositivity**B** Newborn HBV DNA seropositivity**C** Newborn HBeAg seropositivity

Figure 2 Effect of lamivudine treatment vs control (placebo or no intervention) on interruption of hepatitis B virus mother-to-child transmission as indicated by newborn serum hepatitis B surface antigen or hepatitis B virus DNA. Vertical line indicates no difference between compared treatment. Horizontal lines show 95% CIs. Squares indicate point estimates, and the size of the squares indicates the weight of each study in the meta-analysis. HBeAg: Hepatitis B e antigen; HBsAg: Hepatitis B surface antigen; M-H random: Mantel-Haenszel random-effects model; CI: Confidence interval; HBV: Hepatitis B virus; RR: Risk ratio.

plots showed possible publication bias (Figure 2D).

Lamivudine treatment for the mothers receiving

HBIG before delivery significantly interrupted MTCT.

The efficacy of lamivudine *vs* HBIG in interruption

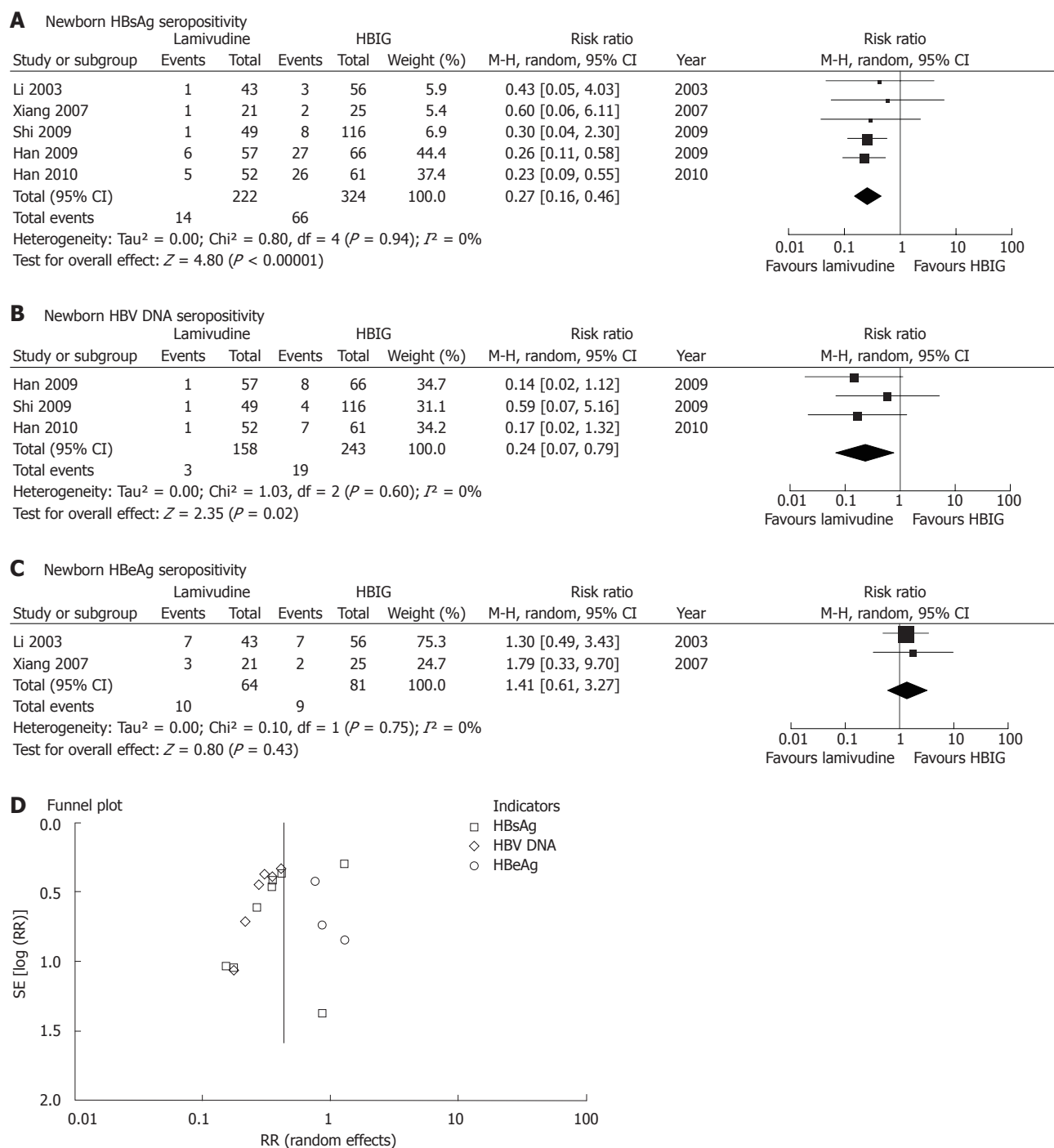


Figure 3 Lamivudine treatment vs hepatitis B immunoglobulin in interruption of hepatitis B virus mother-to-child transmission as indicated by newborn serum hepatitis B surface antigen or hepatitis B virus DNA. CI: Confidence interval; HBIG: Hepatitis B immunoglobulin; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; M-H random: Mantel-Haenszel random-effects model; RR: Risk ratio.

of MTCT indicated by serum HBsAg or HBV DNA was 0.27, 0.16-0.46 in 5 RCTs; $P < 0.01$, with minimum heterogeneity ($P = 0.94$, $I^2 = 0$); and 0.24, 0.07-0.79 in 3 RCTs; $P = 0.02$, with minimum heterogeneity ($P = 0.60$, $I^2 = 0$) (Figure 3A and B). However, the corresponding value indicated by HBeAg was not significant (1.41, 0.61-3.27 in 3 RCTs; $P = 0.43$) with minimum heterogeneity ($P = 0.75$, $I^2 = 0$) (Figure 3C). The funnel plots showed possible publication bias (Figure 3D).

Effect of lamivudine on interruption of MTCT indicated by serum HBsAg or HBV DNA of infants 6-12 mo after birth

Compared with controls (placebo or no treatment), lamivudine treatment significantly interrupted MTCT. The efficacy (RR, 95% CI) of lamivudine treatment *vs* controls was 0.33, 0.21-0.50 in 6 RCTs; $P < 0.01$, with medium heterogeneity ($P = 0.46$, $I^2 = 0$) as shown by serum HBsAg (Figure 4A). It was 0.32, 0.20-0.50 in 4 RCTs; $P < 0.01$, with medium heterogeneity ($P = 0.46$, $I^2 = 0$) as shown by HBV DNA (Figure 4B).

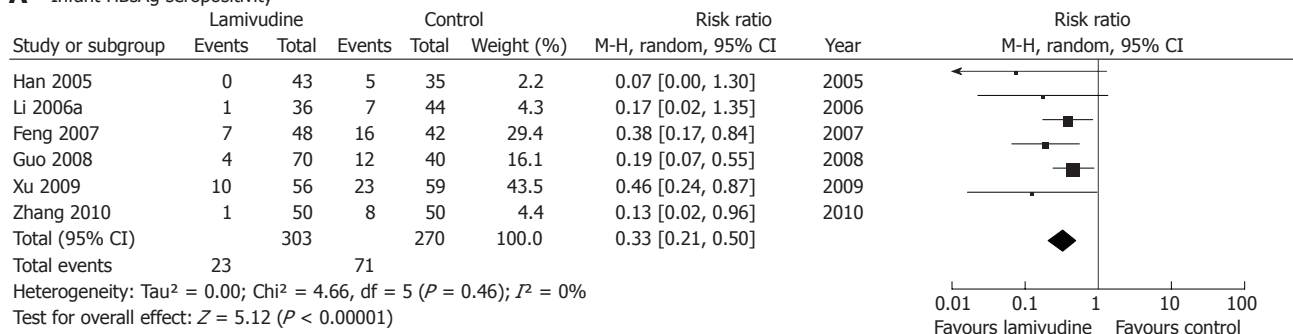
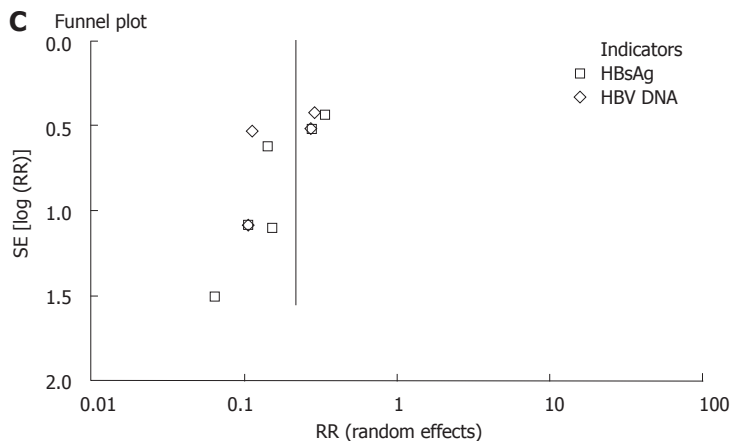
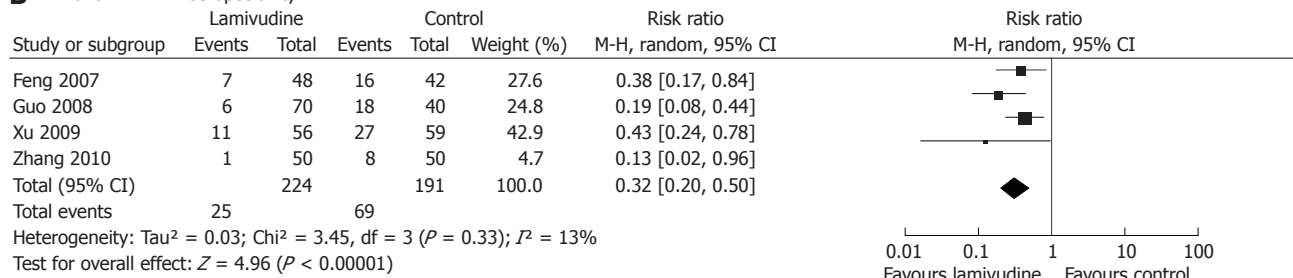
A Infant HBsAg seropositivity**B** Infant HBV DNA seropositivity

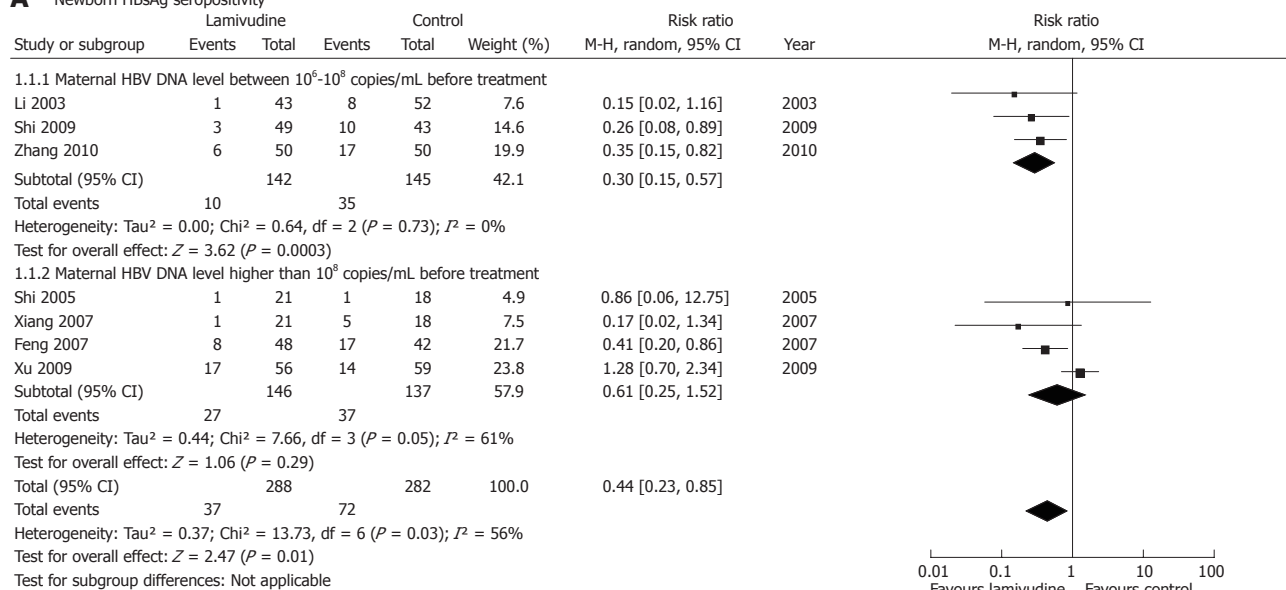
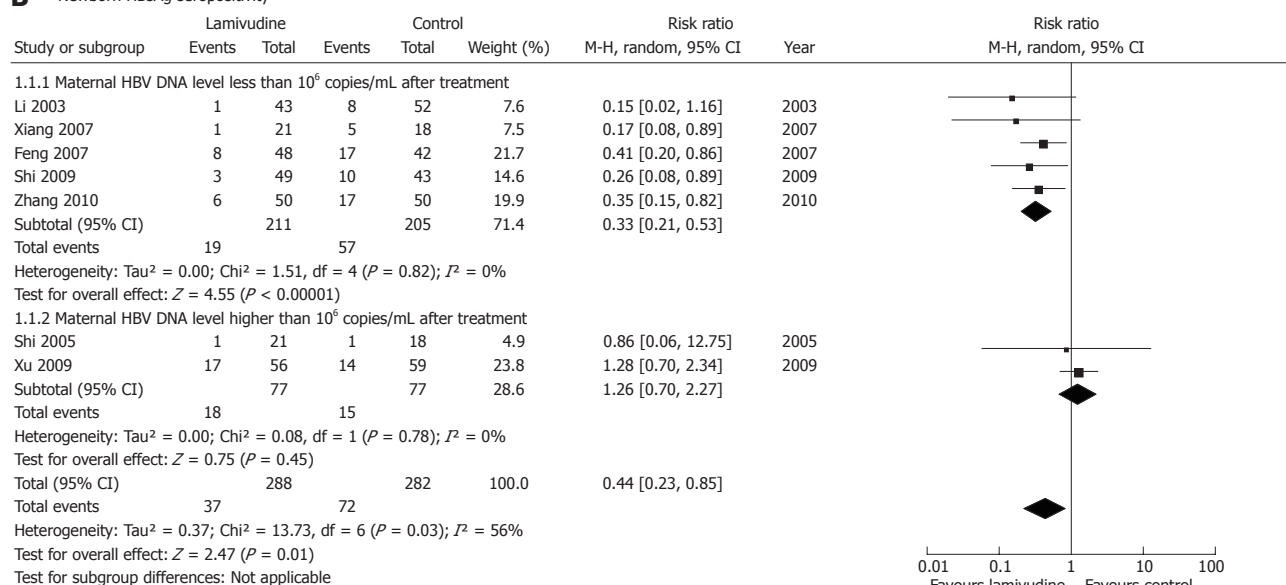
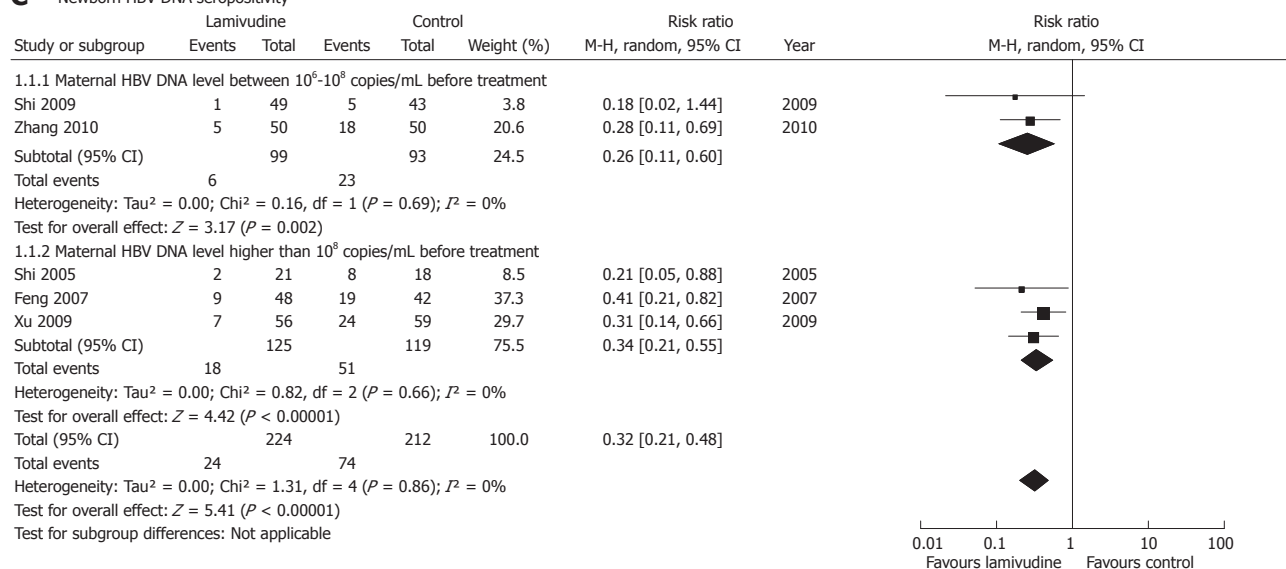
Figure 4 Effects of lamivudine vs control (placebo or no intervention) on interruption of hepatitis B virus mother-to-child transmission as indicated by serum hepatitis B surface antigen or hepatitis B virus DNA of infants 6-12 mo after birth. Vertical line indicates no difference between compared treatment. Horizontal lines show 95% CIs. Squares indicate point estimates, and the size of the squares indicates the weight of each study in the meta-analysis. HBsAg: Hepatitis B surface antigen; M-H random: Mantel-Haenszel random-effects model; CI: Confidence interval; HBV: Hepatitis B virus; RR: Risk ratio.

0.01, with minimum heterogeneity ($P = 0.33$, $I^2 = 13\%$) as shown by serum HBV DNA (Figure 4B). The funnel plots showed possible publication bias (Figure 4C).

Two RCTs evaluated the effect of lamivudine treatment *vs* HBIG in late pregnancy on the interruption of MTCT^[22,23]. The efficacy of lamivudine *vs* HBIG in interruption of MTCT indicated by serum HBsAg or HBV DNA in 2 RCTs was 0.05, 0.01-0.41; $P < 0.01$, with minimum heterogeneity ($P = 0.95$, $I^2 = 0$); and 0.06, 0.01-0.47; $P < 0.01$, with minimum heterogeneity ($P = 0.95$, $I^2 = 0$), respectively. Two RCTs evaluated the efficacy of lamivudine plus HBIG *vs* HBIG alone in the interruption of MTCT indicated by serum HBsAg^[24,32]. The corresponding value was 0.28, 0.13-0.65, $P < 0.01$, with minimum heterogeneity ($P = 0.41$, $I^2 = 0$).

Influence of maternal viral load before or after lamivudine treatment on MTCT indicated by serum HBsAg or HBV DNA of newborns

To determine the effect of viral load of mothers before or after lamivudine treatment on interruption of MTCT, we stratified the included mothers into subgroups with different viral loads and compared with the controls. MTCT was indicated by newborn serum HBsAg. In the mothers with a viral load of 10^6 - 10^8 copies/mL before lamivudine treatment, the efficacy (RR, 95% CI) of lamivudine *vs* controls was 0.30, 0.15-0.57 in 3 RCTs, $P < 0.01$, with minimum heterogeneity ($P = 0.73$, $I^2 = 0$), however, in the mothers with a viral load $> 10^8$ copies/mL before lamivudine treatment, the corresponding value in lamivudine *vs* controls was 0.61, 0.25-1.52 in 4 RCTs, $P = 0.29$, with

A Newborn HBsAg seropositivity**B** Newborn HBsAg seropositivity**C** Newborn HBV DNA seropositivity

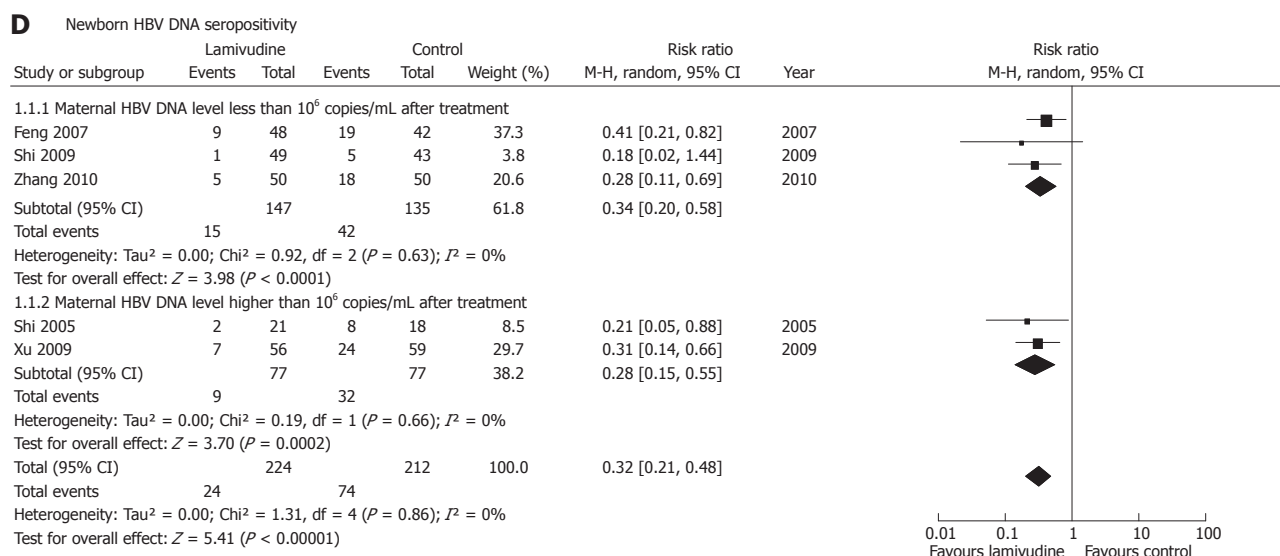


Figure 5 Influence of maternal viral load before or after lamivudine treatment on hepatitis B virus mother-to-child transmission as indicated by serum hepatitis B surface antigen or hepatitis B virus DNA of newborns within 24 h after birth. Vertical line indicates no difference between compared treatments. Horizontal lines show 95% CIs. Squares indicate point estimates, and the size of the squares indicates the weight of each study in the meta-analysis. CI: Confidence interval; HBV: Hepatitis B virus; M-H random: Mantel-Haenszel random-effects model; RR: Risk ratio; HBsAg: Hepatitis B surface antigen.

significant heterogeneity ($P = 0.05$, $I^2 = 61\%$) (Figure 5A). In the mothers with a viral load $< 10^6$ copies/mL after lamivudine treatment, the efficacy of lamivudine treatment *vs* controls was 0.33, 0.21–0.53 in 5 RCTs, $P < 0.01$, with minimum heterogeneity ($P = 0.82$, $I^2 = 0$), however, in the mothers with a viral load $> 10^6$ copies/mL after lamivudine treatment, the corresponding value was 1.26, 0.70–2.27 in 2 RCTs, $P = 0.45$, with minimum heterogeneity ($P = 0.78$, $I^2 = 0$) (Figure 5B). When MTCT was indicated by newborn serum HBV DNA, lamivudine treatment significantly interrupted MTCT in groups with various maternal viral loads before or after lamivudine treatment ($P < 0.01$) (Figure 5C and D).

Effect of lamivudine treatment starting time on interruption of MTCT indicated by serum HBsAg or HBV DNA of newborns within 24h after birth

Lamivudine treatment was initiated from week 28 of gestation in most of the included studies. The treatment was initiated from week 32 of gestation in one study^[25]. The efficacy of lamivudine treatment initiated at week 28 of gestation *vs* controls in interruption of MTCT indicated by serum HBsAg or HBV DNA (RR, 95% CI) was 0.34, 0.22–0.52 in 7 RCTs; $P < 0.01$, with minimum heterogeneity ($P = 0.92$, $I^2 = 0$); and 0.33, 0.22–0.50 in 5 RCTs; $P < 0.01$, with minimum heterogeneity ($P = 0.86$, $I^2 = 0$), respectively. When lamivudine treatment was initiated at week 32 of gestation, MTCT was not significantly interrupted as indicated by serum HBsAg, however, lamivudine significantly interrupt MTCT as shown by serum HBV DNA (Figure 6).

Efficacy of lamivudine treatment in interruption of MTCT indicated by serum HBsAg or HBV DNA of newborns within 24h after birth among different studies

We stratified the included studies into high and low

qualities and evaluated the efficacy of lamivudine in interruption of MTCT. Using pooled data of “low-quality” studies, the efficacy of lamivudine *vs* controls was 0.35, 0.23–0.55 in 6 RCTs; $P < 0.01$, with minimum heterogeneity ($P = 0.88$, $I^2 = 0$ %) indicated by serum HBsAg. It was 0.34, 0.22–0.52 in 4 RCTs; $P < 0.01$, with minimum heterogeneity ($P = 0.81$, $I^2 = 0$ %) indicated by serum HBV DNA. Using pooled data of the 2 “high-quality” studies, the corresponding value was 0.63, 0.13–3.04, $P = 0.57$, with significant heterogeneity ($P = 0.02$, $I^2 = 81\%$) as shown by serum HBsAg. However, the corresponding value was 0.29, 0.14–0.59, $P < 0.01$ with minimum heterogeneity ($P = 0.93$, $I^2 = 0$) as indicated by serum HBV DNA. These results are shown in Figure 7.

Side effects of lamivudine treatment

Three RCTs reported adverse effects of lamivudine in mothers^[25,26,34]. The incidence of adverse effects was not significantly different as compared with the control. Only one trial reported adverse event in the newborns^[25]. Among the ten major adverse events, only one was considered drug-related, with a symptom of jaundice.

DISCUSSION

This meta-analysis included 15 RCTs published up to January 2011, including a total of 1693 HBV-carrier mothers. We demonstrated that lamivudine treatment in the HBV-carrier mothers, as compared with controls, significantly interrupted MTCT as indicated by serum HBsAg or HBV DNA of newborns or infants. And lamivudine treatment *vs* HBIG in the HBV-carrier mothers significantly interrupted MTCT as indicated by serum HBsAg or HBV DNA of newborns or infants. This is also true for lamivudine plus HBIG *vs* HBIG. In a recent meta-analysis, advantage of lamivudine treat-

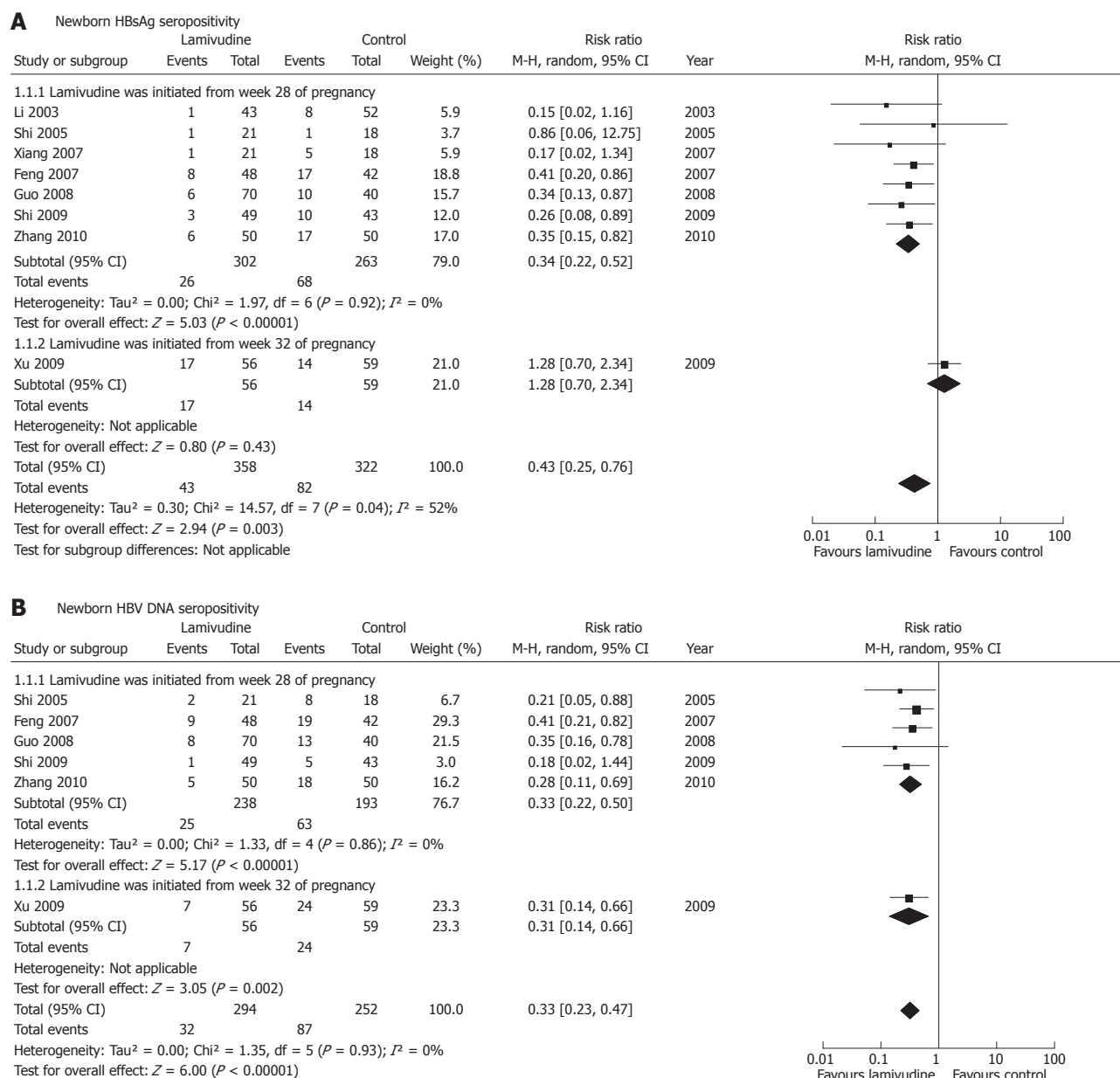


Figure 6 Effect of lamivudine treatment starting time on interruption of mother-to-child transmission indicated by newborn hepatitis B surface antigen or hepatitis B virus DNA. Vertical line indicates no difference between compared treatments. Horizontal lines show 95% CIs. Squares indicate point estimates, and the size of the squares indicates the weight of each study in the meta-analysis. CI: Confidence interval; HBV: Hepatitis B virus; M-H random: Mantel-Haenszel random-effects model; RR: Risk ratio; HBsAg: Hepatitis B surface antigen.

ment was not found over HBIG because two important papers were not included^[15]. This result is quite reasonable because the recommended dose of HBIG might be insufficient to neutralize the huge virus load in HBV-carrier mothers at late pregnancy, although HBIG to HBeAg-seropositive mothers from week 28 of gestation significantly decreased the seropositivity of HBV DNA in newborns^[36]. Thus, lamivudine can be used for the pregnant women with a high degree of infectiousness.

Serum HBsAg, HBeAg, and/or HBV DNA in newborns or infants born to HBV-carrier mothers are routine indicators of MTCT. Of these indicators, HBsAg is a reliable and widely used one. Beasley *et al.*^[37] suggested two criteria for HBV perinatal infection: (1) high titers of

HBsAg within 24 h after birth; and (2) after the joint immunoprophylaxis, infants developed into HBsAg carriers. In addition, continuous monitoring of HBeAg and/or HBV DNA is also suggested, because HBeAg from the mother through the placenta will disappear within 7 mo after birth and peripheral blood HBV DNA testing is more reliable and sensitive than other HBV markers^[38,39]. In this study, although the results using HBsAg or HBV DNA as an indicator were mostly consistent, there were some inconsistencies in indicating MTCT. If indicated solely by HBsAg, lamivudine treatment in the mothers with a viral load $> 10^8$ copies/mL before the treatment or in those with a viral load $> 10^6$ copies/mL after the treatment could not significantly interrupt MTCT. How-

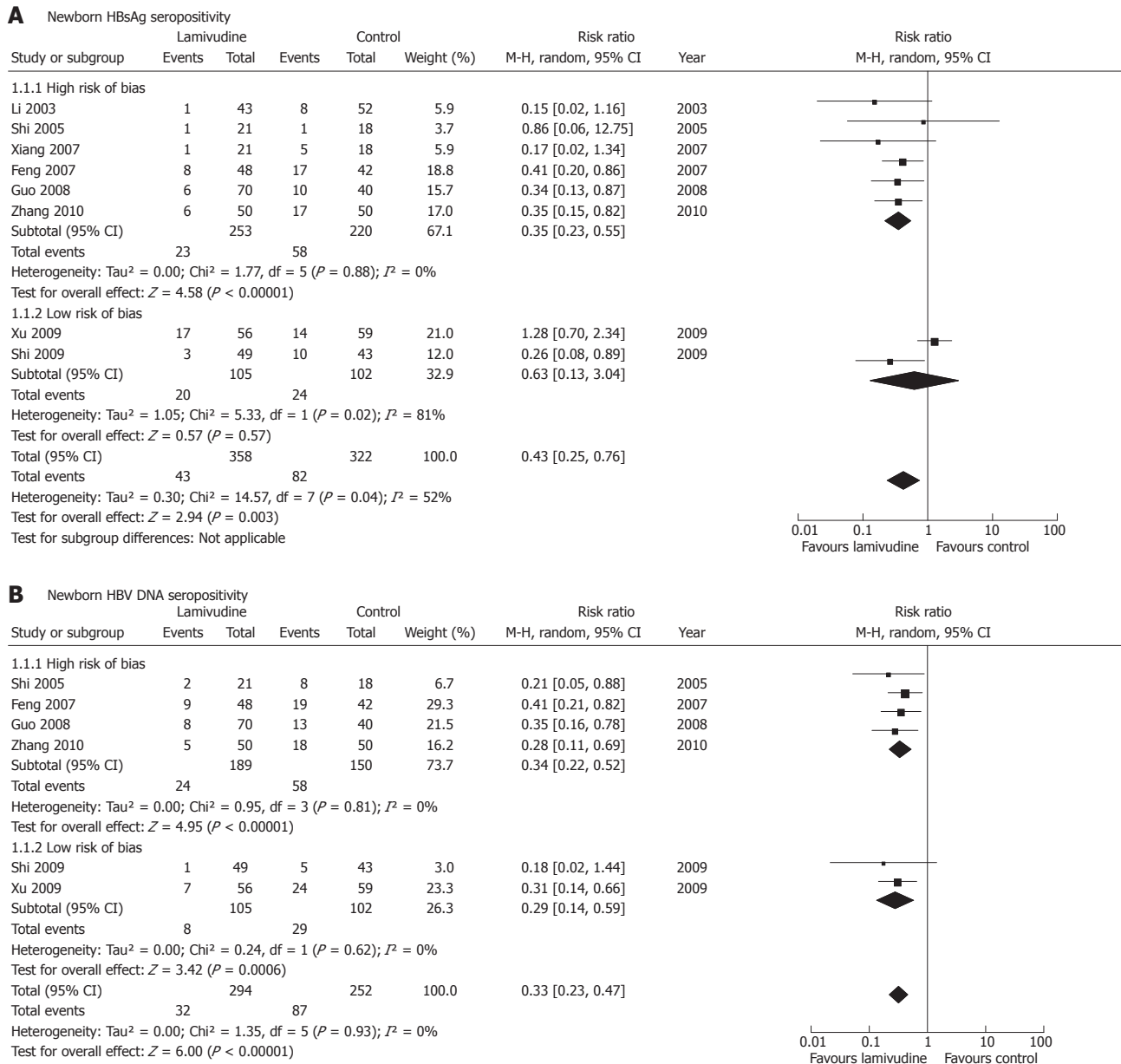


Figure 7 Efficacy of lamivudine treatment in “high-quality” studies or “low-quality” studies in interruption of mother-to-child transmission indicated by serum hepatitis B surface antigen or hepatitis B virus DNA of newborns. Vertical line indicates no difference between compared treatments. Horizontal lines show 95% CIs. Squares indicate point estimates, and the size of the squares indicates the weight of each study in the meta-analysis. CI: Confidence interval; HBV: Hepatitis B virus; M-H random: Mantel-Haenszel random-effects model; RR: Risk ratio; HBsAg: Hepatitis B surface antigen.

ever, if indicated by newborn HBV DNA, lamivudine treatment in the mothers with a viral load $> 10^8$ copies/mL before the treatment or in those with a viral load $> 10^6$ copies/mL after the treatment significantly interrupted MTCT. The same results were found in the pooled analysis of “low quality” and “high quality” studies. These controversial evidences reflect the validity and reliability of the indicators. In the included studies, HBV DNA was measured by quantitative PCR method. However, a viral load $\leq 5 \times 10^2$ copies/mL is usually undetected using commercially available reagents in mainland China. HBV DNA is frequently negative in HBsAg seropositive subjects, especially in asymptomatic HBsAg carriers^[40-42]. Thus, efficacy of lamivudine treatment in

interruption of MTCT might be over-estimated by using newborn HBV DNA alone. Serial examination of HBV DNA and HBsAg from newborns to infants 6-12 mo after birth is highly suggested. In this study, we also found that lamivudine treatment was unable to interrupt transmission of HBeAg from mothers to newborns. HBeAg, a small soluble protein, might pass through the placenta during gestation and disappear within 6-7 mo after birth, indicating that HBeAg is unsuitable for indicating MTCT for newborns, but can be used for the confirmation of MTCT 6-12 mo after birth.

In this study, we confirmed that lamivudine treatment from week 28 of gestation was efficient in interrupting MTCT as indicated by serum HBsAg or HBV DNA of

newborns within 24 h after birth. However, only one study reported that lamivudine treatment from week 32 of gestation was inefficient in interrupting MTCT as indicated by serum HBsAg, although newborn HBV DNA could be significantly decreased. Thus, we suggest that lamivudine treatment should be initiated from week 28 of gestation.

The incidence of adverse effects was not significantly different in HBV carrier mothers with and without lamivudine treatment. Lamivudine treatment in HBV carrier-mothers in late pregnancy has been inversely associated with the complications of HBV-infected pregnant patients^[43]. Thus, lamivudine treatment is well-tolerated and safe for the HBV-carrier mothers at the late stage of pregnancy. However, long-term treatment with lamivudine might generate the treatment-escape mutations like V173L in the B domain and M204V or I substitution in the C domain of the polymerase/reverse transcriptase^[44]. Generation of lamivudine treatment-escape mutations might prevent future treatment of the HBV carrier mothers.

Our meta-analysis has several potential limitations. Firstly, some analysis included few trials so that the subgroup analysis could not be conducted appropriately. Secondly, HBeAg status of mothers was not evaluated because the data was incomplete in the original studies. Thirdly, the majority of included RCTs were of low quality and had high risk of bias in design, and funnel plot showed possible publication bias. The results from this meta-analysis should be discreetly interpreted.

In conclusion, lamivudine treatment in HBV carrier-mothers from 28 wk of gestation efficiently interrupts MTCT as indicated by newborn or infant serum HBsAg or HBV DNA. Lamivudine treatment is safe for the HBV-carrier mothers in late pregnancy and more efficient than HBIG in interrupting MTCT. If maternal viral load is reduced to $< 10^6$ copies/mL by lamivudine treatment, HBV MTCT can be prevented more efficiently as indicated by newborn serum HBsAg.

COMMENTS

Background

Mother-to-child transmission (MTCT) of hepatitis B virus (HBV) is associated with a very high rate of chronicity, especially in countries where HBV is endemic. Prevention of MTCT is the most important strategy in the global eradication of HBV infection. Apart from the joint immunoprophylaxis to infants born to HBV-carrier mothers, lamivudine treatment in late pregnancy has been reported to be effective in interrupting MTCT and safe in pregnant women. However, the sample sizes of these studies were small and results were controversial, which necessitates a meta-analysis by pooling data of more available studies.

Research frontiers

Compared with placebo controls or hepatitis B immunoglobulin (HBIG), lamivudine treatment in late pregnancy significantly interrupted MTCT as indicated by serum hepatitis surface antigen (HBsAg) or HBV DNA of newborns 24h or infants 6-12 mo after birth. In the mothers with viral load $< 10^8$ copies/mL, lamivudine treatment has a clear beneficial effect, as indicated by newborn serum HBsAg. Lamivudine treatment initiated at week 28 of gestation is efficient in interruption of MTCT as indicated by serum HBsAg or HBV DNA of newborns.

Innovations and breakthroughs

A recent meta-analysis of randomized controlled trials using data up to October 2009 has demonstrated that lamivudine treatment in HBV-infected mothers in

late pregnancy effectively prevented MTCT. However, difference in interruption of MTCT between lamivudine treatment and HBIG was not found.

Applications

Lamivudine treatment for HBV carrier mothers should be initiated at week 28 of gestation. For the HBV carrier mothers with viral load $> 10^8$ copies/mL, antiviral treatment with lamivudine alone might be not enough to interrupt MTCT. MTCT might be efficiently interrupted if maternal viral load is decreased to the level of $< 10^6$ copies/mL by lamivudine treatment.

Terminology

MTCT of HBV includes in utero transmission and perinatal transmission of HBV. In East and Southeast Asia, in utero transmission of HBV is rare, whereas perinatal transmission is common.

Peer review

The study determines the effect of lamivudine treatment in hepatitis B virus-carrier mothers in late pregnancy on interruption of MTCT by means of meta-analysis.

REFERENCES

- 1 Lavanchy D. Worldwide epidemiology of HBV infection, disease burden, and vaccine prevention. *J Clin Virol* 2005; **34** Suppl 1: S1-S3
- 2 Petrova M, Kamburov V. Breastfeeding and chronic HBV infection: clinical and social implications. *World J Gastroenterol* 2010; **16**: 5042-5046
- 3 Bai H, Zhang L, Ma L, Dou XG, Feng GH, Zhao GZ. Relationship of hepatitis B virus infection of placental barrier and hepatitis B virus intra-uterine transmission mechanism. *World J Gastroenterol* 2007; **13**: 3625-3630
- 4 Zhang SL, Yue YF, Bai GQ, Shi L, Jiang H. Mechanism of intrauterine infection of hepatitis B virus. *World J Gastroenterol* 2004; **10**: 437-438
- 5 Lee C, Gong Y, Brok J, Boxall EH, Gluud C. Effect of hepatitis B immunisation in newborn infants of mothers positive for hepatitis B surface antigen: systematic review and meta-analysis. *BMJ* 2006; **332**: 328-336
- 6 Ni YH. Natural history of hepatitis B virus infection: pediatric perspective. *J Gastroenterol* 2011; **46**: 1-8
- 7 del Canho R, Grosheide PM, Mazel JA, Heijink RA, Hop WC, Gerards LJ, de Gast GC, Fetter WP, Zwijsen J, Schalm SW. Ten-year neonatal hepatitis B vaccination program, The Netherlands, 1982-1992: protective efficacy and long-term immunogenicity. *Vaccine* 1997; **15**: 1624-1630
- 8 Chotiayaputta W, Lok AS. Role of antiviral therapy in the prevention of perinatal transmission of hepatitis B virus infection. *J Viral Hepat* 2009; **16**: 91-93
- 9 Wen WH, Chen HL, Ni YH, Hsu HY, Kao JH, Hu FC, Chang MH. Secular trend of the viral genotype distribution in children with chronic hepatitis B virus infection after universal infant immunization. *Hepatology* 2011; **53**: 429-436
- 10 Yin J, Zhang H, He Y, Xie J, Liu S, Chang W, Tan X, Gu C, Lu W, Wang H, Bi S, Cui F, Liang X, Schaefer S, Cao G. Distribution and hepatocellular carcinoma-related viral properties of hepatitis B virus genotypes in Mainland China: a community-based study. *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 777-786
- 11 Jonas MM. Hepatitis B and pregnancy: an underestimated issue. *Liver Int* 2009; **29** Suppl 1: 133-139
- 12 van Zonneveld M, van Nunen AB, Niesters HG, de Man RA, Schalm SW, Janssen HL. Lamivudine treatment during pregnancy to prevent perinatal transmission of hepatitis B virus infection. *J Viral Hepat* 2003; **10**: 294-297
- 13 Li XM, Shi MF, Yang YB, Shi ZJ, Hou HY, Shen HM, Teng BQ. Effect of hepatitis B immunoglobulin on interruption of HBV intrauterine infection. *World J Gastroenterol* 2004; **10**: 3215-3217
- 14 Kazim SN, Wakil SM, Khan LA, Hasnain SE, Sarin SK. Vertical transmission of hepatitis B virus despite maternal lamivudine therapy. *Lancet* 2002; **359**: 1488-1489

- 15 **Shi Z**, Yang Y, Ma L, Li X, Schreiber A. Lamivudine in late pregnancy to interrupt in utero transmission of hepatitis B virus: a systematic review and meta-analysis. *Obstet Gynecol* 2010; **116**: 147-159
- 16 **Schulz KF**, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995; **273**: 408-412
- 17 **Moher D**, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, Tugwell P, Klassen TP. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998; **352**: 609-613
- 18 **Higgins JP**, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**: 1539-1558
- 19 **Berlin JA**, Laird NM, Sacks HS, Chalmers TC. A comparison of statistical methods for combining event rates from clinical trials. *Stat Med* 1989; **8**: 141-151
- 20 **Sterne JA**, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol* 2001; **54**: 1046-1055
- 21 **Zhang YF**. The clinical observation of effect of lamivudine on interrupting mother to infant transmission of chronic HBV on 50 mothers [in Chinese]. *J Prat Obst Gynecol* 2010; **26**: 367-368
- 22 **Han Q**. Effect of lamivudine treatment on preventing HBV vertical transmission in pregnant women [in Chinese]. *J Med Theor Prac* 2010; **23**: 631-633
- 23 **Han GR**, Fang ZX, Zhao W, Wang GJ, Wang CM, Tang X, Yue X. Efficacy and safety of lamivudine treatment on preventing hepatitis B virus vertical transmission in pregnant women [in Chinese]. *Chin J Infect Dis* 2009; **27**: 673-676
- 24 **Su TB**, Liu JL. The observation of effect of lamivudine combined with HBIG and HBV vaccine on interrupting mother to infant transmission of chronic HBV [in Chinese]. *Chin J Coal Industry Med* 2009; **12**: 104
- 25 **Xu WM**, Cui YT, Wang L, Yang H, Liang ZQ, Li XM, Zhang SL, Qiao FY, Campbell F, Chang CN, Gardner S, Atkins M. Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multicentre, randomized, double-blind, placebo-controlled study. *J Viral Hepat* 2009; **16**: 94-103
- 26 **Shi ZJ**, Li XM, Yang YB, Ma L. Clinical research on the interruption of mother to child transmission of HBV- a randomized, double-blind, placebo-control study. Unite for Site 6th Annual Global Health Conference. New Haven (CT): Yale University, 2009
- 27 **Yang JH**. The clinical observation of effect of lamivudine on blocking mother to infant transmission of chronic HBV [in Chinese]. *Int Med Health Guid News* 2008; **14**: 76-78
- 28 **Guo YZ**, Li SX, Ge SL, Wang JH. Effect of lamivudine treatment combined with active-passive immunization on interrupting mother to infant transmission of HBV [in Chinese]. *Clin Focus* 2008; **23**: 1730-1731
- 29 **Xiang GJ**, Sun JW, Jiang SQ, Hu XB, Qu AL. Evaluation of therapeutic effect in HBV vertical transmission by lamivudine treatment combined with active-passive immunization for pregnant women [in Chinese]. *Chin Prac Med* 2007; **2**: 14-16
- 30 **Feng HF**, Zhang SF. Effect on interruption of hepatitis B virus vertical transmission by lamivudine [in Chinese]. *J Appl Clin Pediatr* 2007; **22**: 1019-1020
- 31 **Li WF**, Jiang R, Wei Z, Li Y. Clinical effect and safety of lamivudine in interruption of chronic HBV maternal to infant transmission [in Chinese]. *Chin Hepatol* 2006; **11**: 106-107
- 32 **Li G**, Du WJ. The observation of therapeutic effect in interrupting HBV vertical transmission by joint treatment [in Chinese]. *J Wenzhou Med Coll* 2006; **36**: 493-495
- 33 **Han ZH**, Chen YH, Li LW, Sun XW, Sun YG, Zhao H, Su XS. Effect and safety of preventing HBV vertical transmission by lamivudine treatment [in Chinese]. *Chin J Intern Med* 2005; **44**: 378
- 34 **Shi MF**, Li XM, He J, Yang YB, Hou HY, Zhuang YL, Shen HM. Study of Lamivudine in interruption of HBV intrauterine infection [in Chinese]. *Clin Med Chin* 2005; **21**: 77-78
- 35 **Li XM**, Yang YB, Hou HY, Shi ZJ, Shen HM, Teng BQ, Li AM, Shi MF, Zou L. Interruption of HBV intrauterine transmission: a clinical study. *World J Gastroenterol* 2003; **9**: 1501-1503
- 36 **Xu Q**, Xiao L, Lu XB, Zhang YX, Cai X. A randomized controlled clinical trial: interruption of intrauterine transmission of hepatitis B virus infection with HBIG. *World J Gastroenterol* 2006; **12**: 3434-3437
- 37 **Beasley RP**, Hwang LY, Lee GC, Lan CC, Roan CH, Huang FY, Chen CL. Prevention of perinatally transmitted hepatitis B virus infections with hepatitis B virus infections with hepatitis B immune globulin and hepatitis B vaccine. *Lancet* 1983; **2**: 1099-1102
- 38 **Wang JS**, Chen H, Zhu QR. Transformation of hepatitis B serologic markers in babies born to hepatitis B surface antigen positive mothers. *World J Gastroenterol* 2005; **11**: 3582-3585
- 39 **Zhang SL**, Han XB, Yue YF. Relationship between HBV viremia level of pregnant women and intrauterine infection: nested PCR for detection of HBV DNA. *World J Gastroenterol* 1998; **4**: 61-63
- 40 **Yin J**, Xie J, Liu S, Zhang H, Han L, Lu W, Shen Q, Xu G, Dong H, Shen J, Zhang J, Han J, Wang L, Liu Y, Wang F, Zhao J, Zhang Q, Ni W, Wang H, Cao G. Association between the various mutations in viral core promoter region to different stages of hepatitis B, ranging of asymptomatic carrier state to hepatocellular carcinoma. *Am J Gastroenterol* 2011; **106**: 81-92
- 41 **Yin J**, Xie J, Zhang H, Shen Q, Han L, Lu W, Han Y, Li C, Ni W, Wang H, Cao G. Significant association of different preS mutations with hepatitis B-related cirrhosis or hepatocellular carcinoma. *J Gastroenterol* 2010; **45**: 1063-1071
- 42 **Yin JH**, Zhao J, Zhang HW, Xie JX, Li WP, Xu GZ, Shen J, Dong HJ, Zhang J, Wang L, Han JK, Wang HY, Cao GW. HBV genotype C is independently associated with cirrhosis in community-based population. *World J Gastroenterol* 2010; **16**: 379-383
- 43 **Su GG**, Pan KH, Zhao NF, Fang SH, Yang DH, Zhou Y. Efficacy and safety of lamivudine treatment for chronic hepatitis B in pregnancy. *World J Gastroenterol* 2004; **10**: 910-912
- 44 **Cao GW**. Clinical relevance and public health significance of hepatitis B virus genomic variations. *World J Gastroenterol* 2009; **15**: 5761-5769

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