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Antiviral Therapy in Chronic Hepatitis B Viral Infection During Pregnancy: A Systematic Review and Meta-Analysis

Robert S. Brown, Jr.,[1] Brian J. McMahon,[2] Anna S.F. Lok,[3] John B. Wong,[4] Ahmed T. Ahmed,[5,6] Mohamed A. Mouchli,[7] Zhen Wang,[5,6] Larry J. Prokop,[8] Mohammad Hassan Murad,[5,6,9] and Khaled Mohammed[5,6,9]

Perinatal or mother-to-child transmission (MTCT) of hepatitis B virus (HBV) remains the major risk factor for chronic HBV infection worldwide. In addition to hepatitis B immune globulin and vaccination, oral antiviral therapies in highly viremic mothers can further decrease MTCT of HBV. We conducted a systematic review and meta-analysis to synthesize the evidence on the efficacy and maternal and fetal safety of antiviral therapy during pregnancy. A protocol was developed by the American Association for the Study of Liver Diseases guideline writing committee. We searched multiple databases for controlled studies that enrolled pregnant women with chronic HBV infection treated with antiviral therapy. Outcomes of interest were reduction of MTCT and adverse outcomes to mothers and newborns. Study selection and data extraction were done by pairs of independent reviewers. We included 26 studies that enrolled 3622 pregnant women. Antiviral therapy reduced MTCT, as defined by infant hepatitis B surface antigen seropositivity (risk ratio = 0.3, 95% confidence interval 0.2-0.4) or infant HBV DNA seropositivity (risk ratio = 0.3, 95% confidence interval 0.2-0.5) at 6-12 months. No significant differences were found in the congenital malformation rate, prematurity rate, and Apgar scores. Compared to control, lamivudine or telbivudine improved maternal HBV DNA suppression at delivery and during 4-8 weeks' postpartum follow-up. Tenofovir showed improvement in HBV DNA suppression at delivery. No significant differences were found in postpartum hemorrhage, cesarean section, and elevated creatinine kinase rates. *Conclusions:* Antiviral therapy improves HBV suppression and reduces MTCT in women with chronic HBV infection with high viral load compared to the use of hepatitis B immunoglobulin and vaccination alone; the use of telbivudine, lamivudine, and tenofovir appears to be safe in pregnancy with no increased adverse maternal or fetal outcome. (HEPATOLOGY 2016;63:319-333)

Chronic hepatitis B viral (HBV) infection remains an important global health problem. Up to 600,000 of the approximately 240 million carriers worldwide die annually due to chronic hepatitis B (CHB)-related disease.[1] Perinatal or mother-to-child transmission (MTCT) is the most common form of transmission of HBV in many high-prevalence areas[2,3] and may occur in up to 90% of mothers who are hepatitis B surface antigen (HBsAg)-positive and hepatitis B e antigen (HBeAg)-positive in the absence of

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; CHB, chronic hepatitis B; CI, confidence interval; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus; MTCT, mother-to-child transmission; RCT, randomized controlled trial; RR, risk ratio.

From the [1]Division of Gastroenterology and Hepatology, Weill Cornell Medical College, New York, NY; [2]Liver Diseases and Hepatitis Program, Alaska Native Tribal Health Consortium, Anchorage, AK; [3]Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, MI; [4]Division of Clinical Decision Making, Tufts Medical Center, Boston, MA; [5]Evidence-Based Practice Research Program, [6]Center for the Science of Health Care Delivery, [7]Division of Hospital Internal Medicine, [8]Library Public Services, and [9]Division of Preventive, Occupational and Aerospace Medicine, Mayo Clinic, Rochester, MN

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prophylaxis.[4] This high rate of transmission may be partially due to the high proportion of mothers with active replication and HBeAg positivity during reproductive years,[5-8] particularly in Asian countries and regions of the world where HBV genotype C is found[9] as MTCT is associated with high maternal viral load (HBV DNA $>10^6$ IU/mL).[10-13] Universal prenatal testing of women is therefore recommended, as are hepatitis B vaccination and hepatitis B immunoglobulin administration starting at birth to prevent transmission to the newborn.

Women in their childbearing years with CHB may need antiviral therapy independent of its impact on MTCT if they have immune active HBV infection. Accordingly, data on the safety of antivirals during pregnancy, and especially their impact on potential teratogenicity, are of paramount importance when counseling pregnant patients with CHB on risks and benefits to their offspring.

Antiviral therapies for CHB have advanced markedly in the last decade. The newer, more potent nucleos(t)ide analogues durably suppress HBV viremia in most patients. Evolving data for CHB patients show low (0%-1%) rates of viral resistance and breakthrough after up to 6 years of entecavir or tenofovir monotherapy.[14,15] The benefits of long-term viral suppression include slowing of liver disease progression and reversal of fibrosis and cirrhosis.[16-18] Although no HBV therapies are currently approved for use in pregnancy, women being treated for CHB may become pregnant. Moreover, pregnant women in the immune tolerant phase of CHB with high HBV DNA levels ($>10^6$ IU/mL) may want to be considered for antiviral therapy to reduce the HBV DNA level and decrease the risk of MTCT that can occur despite neonatal immunoprophylaxis.[10,19] Safety data on the use of anti-HBV therapies are largely derived from human immunodeficiency virus (HIV)-positive mothers studied in the Antiretroviral Pregnancy Registry, which do not report any adverse impact of lamivudine or tenofovir use.[20] However, the use of antiviral therapies in pregnancy is controversial, and knowledge about the harm and benefit ratio is not widely disseminated among hepatologists and other providers including those specializing in women's health. Therefore, the American Association for the Study of Liver Diseases (AASLD) made this issue a priority for clinical practice guideline development and evidence synthesis. We performed a systematic review and meta-analysis to compare the effect of oral HBV therapy (lamivudine, entecavir, telbivudine, or tenofovir) on MTCT prevention, HBV DNA suppression, and maternal and fetal safety including major birth defect rates.

Materials and Methods

This systematic review follows a protocol developed by a guideline writing group from the AASLD and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[21]

Eligibility Criteria. We included controlled or comparative studies that enrolled pregnant women diagnosed with chronic HBV infection (characterized by the presence of HBsAg for more than 6 months), who received antiviral therapy and reported the outcomes of interest, including prevention of MTCT of HBV, clinical efficacy, and adverse outcomes from antiviral therapy to both mothers and newborns. Both English and non-English-language studies were included. We excluded studies that enrolled infants who did not receive immunization during the first week postpartum; studies of patients coinfected with hepatitis C, hepatitis D, or HIV; patients receiving steroids, chemotherapy/immunotherapy, liver transplantation, and hemodialysis; and uncontrolled studies or studies published as abstracts only.

Search Strategy. A comprehensive search of Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, and Scopus was conducted from early 1988 to September 11, 2014. The search strategy was designed and conducted by an experienced librarian (L.J.P.) with input from the principal investigator. Controlled vocabulary supplemented with keywords was used to search for studies of antivirals for hepatitis B in pregnancy. Details of the search strategy are available in Supporting Table 1. A manual search of bibliographies of the included studies and relevant systematic reviews was conducted. Content experts from the AASLD were also queried for potential references.

Address reprint requests to: Robert S. Brown, Jr., M.D., M.P.H., Division of Gastroenterology and Hepatology, Weill Cornell Medical College, 1305 York Avenue, 4th Floor New York, NY 10021. E-mail: rsb2005@med.cornell.edu; tel: +1-646-962-5330.

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Study Selection. Two independent reviewers screened titles and abstracts for potential eligibility in duplicate using an online reference management system (DistillerSR; Evidence Partners, Inc.). Included abstracts were then reviewed in full text following the same procedure. Disagreements were reconciled by consensus or by a third reviewer.

Data Extraction. For each study, data extraction was done in duplicate using a standardized, pretested form. A third reviewer compared data and resolved inconsistencies by referring to the full text of the articles. We extracted the following data from each study: study characteristics, patient baseline characteristics, intervention details, and outcomes of interest.

Outcomes. We were interested in the following outcomes: infant outcomes including the risk of MTCT transmission, defined by HBsAg seropositivity at 6-12 months or HBV DNA positivity at 6-12 months; Apgar score (1 minute); prematurity rate; and congenital malformation rate. Maternal outcomes included HBV DNA suppression, alanine aminotransferase (ALT) normalization, HBeAg loss, HBeAg seroconversion, cesarean section rate, postpartum hemorrhage rate, and elevated creatine kinase.

Risk of Bias Assessment. Two reviewers independently assessed the risk of bias (i.e., systematic error) using the Cochrane Risk of Bias assessment tool and the Newcastle-Ottawa Scale for randomized controlled trials (RCTs) and observational studies, respectively. The quality of evidence (i.e., certainty in the estimates) was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation approach. Criteria used to evaluate quality of evidence were risk of bias, indirectness (surrogate outcomes), imprecision (wide confidence intervals), inconsistency (heterogeneity), and publication bias.[22]

Statistical Analysis. For dichotomized outcomes, we calculated the risk ratio (RR) and 95% confidence intervals (CIs) using binomial distribution. We then pooled the log-transformed RRs using the DerSimonian and Laird random-effect models and estimated heterogeneity using the Mantel-Haenszel model. For continuous outcomes, we calculated the weighted difference in means between the baseline and the longest duration of follow-up for each study and the pooled effect size using the DerSimonian and Laird random-effect model. To measure the overall heterogeneity across the included studies, we used the I^2 statistic, where $I^2 > 50\%$ suggests high heterogeneity. All statistical analyses were conducted using STATA, version 13 (StataCorp LP, College Station, TX). We planned to explore the impact of publication bias using the Egger regression asymmetry test and constructing funnel plots if a sufficient number of studies (>20) per outcome was available and heterogeneity was low.[23]

Results

The initial search resulted in 734 citations and three systematic reviews[19,24,25] that included the China Biological Medicine Database and summarized additional studies published in Chinese. We eventually included 26 studies. The average weighted kappa for study selection was 0.82. The study selection process and reasons for exclusions are depicted in Fig. 1.

Characteristics of the Included Studies. Twenty-six studies that enrolled a total of 3622 pregnant women were included in the analysis: 10 studies[26-35] were RCTs and 16 studies[36-51] were nonrandomized studies. Most of the studies (92%) were conducted in China, and none were conducted in the United States. Treatment started in the second or third trimester with an average baseline HBV DNA level of 7.63 log10 IU/mL and an average baseline ALT level of 37.7 U/L. In these studies, all infants received hepatitis B vaccine at birth. Table 1 summarizes the characteristics of the studies.

Among the included studies, 11 compared lamivudine versus control, nine[26,35,36,42-44,48,49,51] compared telbivudine versus control, two[36,51] compared lamivudine versus telbivudine, three[37,38,50] compared tenofovir versus control, and another[37] compared tenofovir versus lamivudine.

Five RCTs[27-29,31,34] were considered to have low risk of bias, while five studies[26,30,32,33,35] were considered to have a high risk of bias due to unclear/unreported methods of randomization, allocation concealment, blinding, or incomplete outcome data reporting. For nonrandomized studies, the overall methodological quality and features were adequate or appropriate as 60% of the studies reported adequate patient selection methods, comparable study groups, and adequate outcome measures and follow-up data. Tables 2 and 3 include detailed descriptions of the risk of bias assessment.

Infant Outcomes. Use of any antiviral therapy compared to control in pregnant women reduced the likelihood of MTCT as defined by infant HBsAg seropositivity (eight RCTs, RR = 0.3, 95% CI 0.2-0.4, I^2 = 63.9%) or infant HBV DNA positivity (five RCTs, RR = 0.3, 95% CI 0.2-0.5, I^2 = 47.2%) at 6-12 months (Fig. 2). Use of any antiviral compared to control reduced the risk of infant HBsAg seropositivity and HBV DNA positivity by 13.4% and 18.7%, respectively. The quality of evidence was moderate to low, rated down due to risk of bias. This significant reduction persisted when comparing individual drugs versus

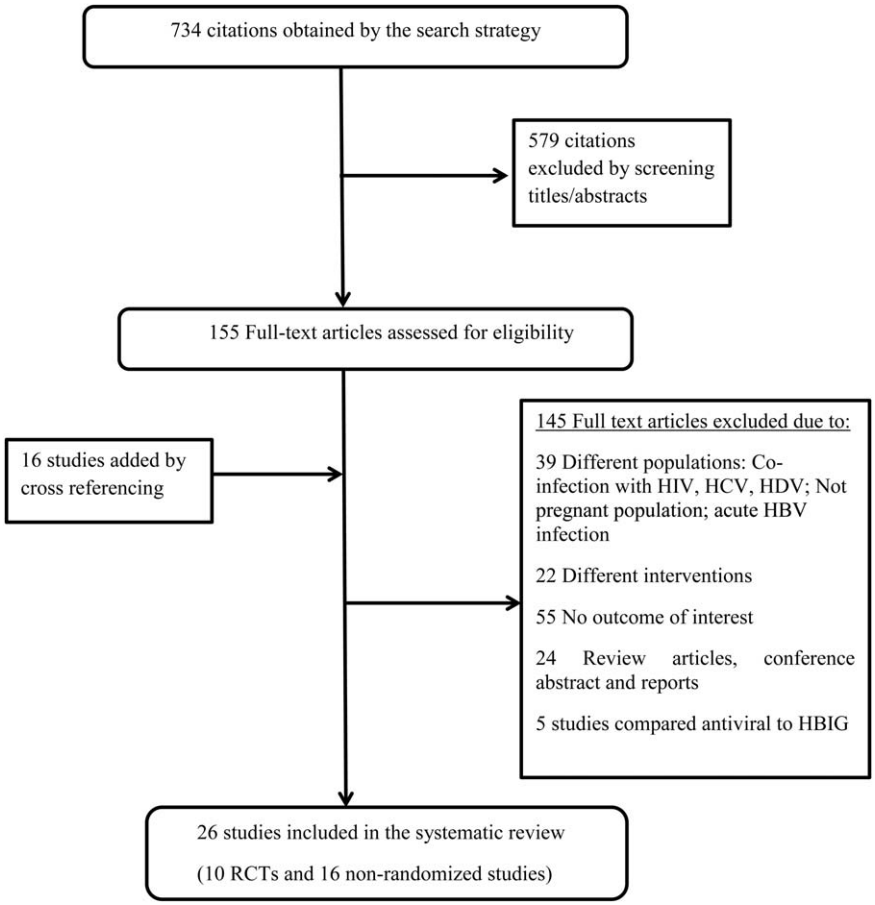

Fig. 1. The study selection process. Abbreviations: HBIG, hepatitis B immunoglobulin; HCV, hepatitis C virus; HDV, hepatitis D virus.

control at 6-12 months after birth. Lamivudine (Fig. 3) reduced infant HBsAg seropositivity by 11.7% (five RCTs, RR = 0.3, 95% CI 0.2-0.6, I^2 = 42.4%) and infant HBV DNA positivity by 21.2% (three RCTs, RR = 0.3, 95% CI 0.2-0.6, I^2 = 47.9%). Telbivudine also reduced infant HBsAg seropositivity by 15.8% (four RCTs, RR = 0.2, 95% CI 0.1-0.5, I^2 = 0%) and infant HBV DNA positivity by 16.2% (two RCTs, RR = 0.1, 95% CI 0.03-0.6, I^2 = 62.4%) compared to the control group (Fig. 4).

In three nonrandomized studies,[37,38,50] tenofovir versus control (Fig. 5) reduced infant HBsAg seropositivity by 15.8% at 6-12 months' follow-up (RR = 0.2, 95% CI 0.1-0.7, I^2 = 0%).

Compared to lamivudine, telbivudine (one study, RR = 1, 95% CI 0.7-1.5) and tenofovir (one study, RR = 2.93, 95% CI 0.12-70.08) showed no statistically significant reduction in infant HBsAg seropositivity at 6-12 months.

When comparing any antiviral therapy versus control for fetal harms, no statistically significant difference was found in any of the non-RCTs reporting on congenital malformation rate, prematurity rate, and Apgar scores (Fig. 6). The quality of the evidence of infant outcomes was moderate to low, down-rated due to risk of bias and imprecision.

Maternal Outcomes. Compared to control, lamivudine improved maternal HBV DNA suppression before delivery (one cohort, RR = 57.1, 95% CI 3.5-921.4) and during 4-8 weeks' postpartum follow-up (two cohorts, RR = 70.9, 95% CI 8.5-590, I^2 = 12.2%). No significant difference was found in maternal ALT normalization.

In studies comparing telbivudine versus control, telbivudine showed improved maternal HBV DNA suppression at delivery (three cohorts, RR = 52.8, 95% CI 10.7-261.8, I^2 = 0%), at 4 weeks postpartum (two cohorts, RR = 102, 95% CI 14.4-722.8, I^2 = 0%), and at 28 weeks postpartum (one cohort, RR = 1.5, 95% CI 1.2-1.8). When compared to control, pregnant women receiving telbivudine consistently had improved maternal ALT normalization at delivery (two cohorts, RR = 1.5, 95% CI 1.2-1.8, I^2 = 0%), at 4 weeks postpartum (one cohort, RR = 1.6, 95% CI 1.1-2.3), and at 28 weeks postpartum (one cohort, RR = 1.3, 95% CI 1.04-1.6). Telbivudine also significantly increased maternal HBeAg loss at delivery (two cohorts, RR = 1.7, 95% CI 1.3-2.2, I^2 = 0%), at 4 weeks postpartum

Table 1. Characteristics of the Included Studies

Author, Year	Interventions	Participants (Mothers) (N)	Country	Age (Years)	Baseline HBV DNA Level (Log10 IU/mL)	Baseline ALT Level (U/L)	Treatment Start (Gestational Weeks)	Treatment Discontinuation (Postpartum Weeks)	HBIG + Vaccine (Infants)	Study Design
Zhang and Wang, 2009[26]	Telbivudine	31	China	20-40	7.4 ± 0.8	NR	32-36	NR	All	RCT
	Control group	30		20-40	7.5 ± 0.5	NR	NA	NA		
Xu et al., 2009[27]	Lamivudine	89	China	26 (19-32)	8.6 ± 0.2	0.4 (0.1-5.3) ×ULN	32	4	HBV vaccine with or without HBIG	RCT
	Control group	61		25 (20-36)	8.7 ± 0.2	0.4 (0.1-6) ×ULN	NA	NA		
Yang et al., 2008[28]	Lamivudine	20	China	20-40	NR	NR	28	4	All	RCT
	Control group	20		20-40	NR	NR	NA	NA		
Li et al., 2003[29]	Lamivudine	43	China	20-40	7.5 ± 0.5	NR	28	4	All	RCT
	Control group	52		20-40	7.1 ± 1.3	NR	NA	NA		
Zhang, 2010[30]	Lamivudine	50	China	NR	6.8 ± 0.9	NR	28	4	All	RCT
	Control group	50		NR	6.9 ± 1.7	NR	NA	NA		
Shi et al., 2009[31]	Lamivudine	49	China	NR	7.2 ± 1.9	NR	28	4	All	RCT
	Control group	43		NR	6.4 ± 2.1	NR	NA	NA		
Guo et al., 2008[32]	Lamivudine	70	China	NR	NR	NR	28	4	All	RCT
	Control group	40		NR	NR	NR	NA	NA		
Xiang et al., 2007[33]	Lamivudine	21	China	NR	8.0 ± 1.2	NR	28	4	All	RCT
	Control group	18		NR	7.2 ± 0.8	NR	NA	NA		
Shi et al., 2005[34]	Lamivudine	21	China	NR	8.7 ± 0.7	NR	28	4	All	RCT
	Control group	18		NR	8.9 ± 1.1	NR	NA	NA		
Guo et al., 2011[35]	Telbivudine	28	China	NR	7.7 ± 4.6	NR	28	4	All	RCT
	Control group	26		NR	7.9 ± 3.5	NR	NA	NA		
Zhang et al., 2014[36]	Telbivudine	252	China	29.8 ± 6.3	6.9 ± 0.4	30.1 ± 27.9	28-30	4	All	Prospective, open-label, interventional trial
	Lamivudine	51		28.4 ± 7.1	6.9 ± 0.4	39.7 ± 26.4	28-30	4		
	Control group	352		28.9 ± 4.6	6.8 ± 0.5	29.5 ± 20.7	NA	NA		
Greenup et al., 2014[37]	Tenofovir	58	Australia	30.0 ± 8.5	7.9 ± 0.8	28 (22-36)	32	12	All	Cohort study
	Lamivudine	52		28.0 ± 5.3	7.7 ± 0.6	22 (18-30)	32	4		
	Control group	20		28.0 ± 5.0	8 ± 0.04	25 (17-31)	NA	NA		
Celen et al., 2013[38]	Tenofovir	21	Turkey	28.2 ± 4.1	8.3	56 (22-71)	18-27	4	All	Retrospective study
	Control group	24		26.9 ± 2.9	8.3	52 (19-77)	NA	NA		
Jiang et al., 2012[39]	Lamivudine	164	China	27.3 ± 4.4	7.8 ± 0.8	39.6 ± 26.0	24-32	At delivery	All	Cohort study
	Control group	92		26.4 ± 3.2	7.9 ± 0.6	42.2 ± 0.4	NA	NA		
Chen et al., 2012[40]	Lamivudine	75	China	NR	7.7 ± 0.5	NR	24-32	4	All	Cohort study
	Control group	28		NR	7.3 ± 0.4	NR	NA	NA		
Yu et al., 2012[41]	Lamivudine	94	China	26.4 ± 4.2	6.9 ± 0.4	45.0	24-32.	Continued for variable duration after delivery	All	Cohort study
	Control group	91		25.8	7.0 ± 0.6	45.0	NA	NA		
Pan et al., 2012[42]	Telbivudine	53	China	27 (21-34)	8.08 (6.6-9.4)	60.4 (41.4-422)	12-30	Continued for variable duration after delivery	All	Prospective, non-randomized open-label trial
	Control group	35		27 (21-33)	8.1 (6.8-9.1)	63.2 (42.4-262.5)	NA	NA		
Han et al., 2012[43]	Telbivudine	120	China	26.0 ± 3.5	7.3 ± 0.5	31.0 ± 32.2	20-32	4	All	Cohort study
	Control group	100		26.4 ± 3.2	7.3 ± 0.6	31.5 ± 35.1	NA	NA		
Han et al., 2011[44]	Telbivudine	135	China	27 (20-38)	7.4 ± 0.6	35.7 ± 43.4	20-32	4	All	Cohort study

Table 1. *Continued*

Author, Year	Interventions	Participants (Mothers) (N)	Country	Age (Years)	Baseline HBV DNA Level (Log10 IU/mL)	Baseline ALT Level (U/L)	Treatment Start (Gestational Weeks)	Treatment Discontinuation (Postpartum Weeks)	HBIG + Vaccine (Infants)	Study Design
	Control group	94		26 (20-35)	7.3 ± 0.6	42.5 ± 40.1	NA	NA		
Feng, 2007[45]	Lamivudine	48	China	NR	8.3 ± 1.2	NR	28	4	All	RCT
	Control group	42		NR	8.3 ± 1.9	NR	NA	NA		
Li et al., 2006[46]	Lamivudine	36	China	NR	6.9 ± 0.8	NR	28	4	All	RCT
	Control group	44		NR	> 5.00	NR	NA	NA		
Han et al., 2005[47]	Lamivudine	43	China	NR	7.2 ± 0.9	NR	28	4	All	RCT
	Control group	35		NR	> 5.6	NR	NA	NA		
Zhang, 2010[49]	Telbivudine	60	China	NR	NR	NR	28	4	All	RCT
	Control group	60		NR	NR	NR	NA	NA		
Yao et al., 2011[48]	Telbivudine	28	China	NR	7.5 ± 0.6	NR	28	4	All	RCT
	Control group	30		NR	7.5 ± 0.7	NR	NA	NA		
Chen et al., 2015[50]	Tenofovir	62	Taiwan	32.5 ± 3.2	8.2 ± 0.5	16.6 ± 14.4	28	4	All	Open-labeled, nonrandomized controlled trial
	Control group	56		32.4 ± 3.1	8.2 ± 0.4	23.3 ± 36.2	NA	NA		
Yu et al., 2014[51]	Telbivudine	233	China	26.8 ± 3.9	7.8 ± 0.8	57.6 ± 83.5	8-32	At delivery	All	Cohort study
	Lamivudine	154		26.7 ± 3.5	7.7 ± 0.7	56.3 ± 82.7	NA	NA		

Abbreviation: HBIG, hepatitis B immunoglobulin

Table 2. Risk of Bias Assessment for the Included RCTs

Author, Year	Sequence Generation	Allocation Concealment	Blinding of Participants, Personnel, and Assessors	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias	Risk of Bias
Zhang and Wang, 2009[26]	Unclear	Unclear	Unclear	No missing outcome	All prespecifiedoutcomesreported	No	Unclear
Xu et al., 2009[27]	Unclear	Sequentially numbered drug containers of identical appearance	Adequate blinding	One arm of datamissing forethics	All prespecifiedoutcomesreported	No	Low
Yang et al., 2008[28]	Random number table	Sequentially numbereddrug containers ofidentical appearance	Adequate blinding	No missingoutcome data	All prespecified	No	Low
Li et al., 2003[29]	Computer randomnumber generator	Unclear	Measurement notinfluenced by lackof blinding	No missingoutcome data	All prespecifiedoutcomesreported	No	Low
Zhang, 2010[30]	Unclear	Unclear	Unclear	Unclear	None	None	Unclear
Shi et al., 2009[31]	Computer random number generator	Sequentially numbered drug containers of identical appearance	Adequate blinding	Missing outcomeshave no impacton effect size	All prespecifiedoutcomesreported	No	Low
Guo et al., 2008[32]	Adequate	Unclear	Unclear	No missing outcome	All prespecifiedoutcomesreported	No	Unclear
Xiang et al., 2007[33]	Adequate	Unclear	Unclear	No missing outcome	All prespecifiedoutcomesreported	No	Unclear
Shi et al., 2005[34]	Random table	Unclear	Measurement notinfluenced by lackof blinding	No missingoutcome data	All prespecifiedoutcomesreported	No	Low
Guo et al., 2011[35]	Unclear	Unclear	No blinding	No missingoutcome data	All prespecifiedoutcomesreported	No	High/unclear

Table 3. Risk of Bias Assessment for the Observational Studies

	Selection		Comparability		Outcome	
Author, Year	Representativeness of the Exposed Cohort	Selection of the Nonexposed Cohort	Comparability of Cohorts on the Basis of the Design or Analysis	Assessment of Outcome	Was Follow-Up Long Enough for Outcomes to Occur	Adequacy of Follow-Up of Cohorts
Zhang et al., 2014[36]	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Study controls for any additional factors	Record linkage	Yes	Adequate
Greenup et al., 2014[37]	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Study controls for any additional factors	Record linkage	Yes	Adequate
Celen et al., 2013[38]	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Study controls for most important factor	Record linkage	Yes	Adequate
Jiang et al., 2012[39]	No description	Drawn from the same community as the exposed cohort	Study controls for most important factor	No description	Yes	Adequate
Chen et al., 2012[40]	No description	Drawn from the same community as the exposed cohort	Study controls for most important factor	No description	No	Unclear
Yu et al., 2012[41]	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Study controls for most important factor	Record linkage	Yes	Adequate
Pan et al., 2012[42]	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Study controls for most important factor	Record linkage	Yes	Adequate
Han et al., 2012[43]	No description	Drawn from the same community as the exposed cohort	Study controls for most important factor	No description	Unclear	unclear
Han et al., 2011[44]	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Study controls for most important factor	Record linkage	Yes	Adequate
Feng, 2007[45]	No description	No description	No description	No description	No description	No description
Li et al., 2006[46]	No description	No description	No description	No description	No description	No description
Han et al., 2005[47]	No description	No description	No description	No description	No description	No description
Yao et al., 2011[48]	No description	No description	No description	No description	No description	No description
Zhang, 2010[49]	No description	No description	No description	No description	No description	No description
Chen et al., 2015[50]	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Study controls for any additional factors	Record linkage	Yes	Adequate
Yu et al., 2014[51]	Somewhat representative of the community or population	Drawn from the same community as the exposed cohort	Study controls for most important factor	Independent blind assessment	Yes	Adequate

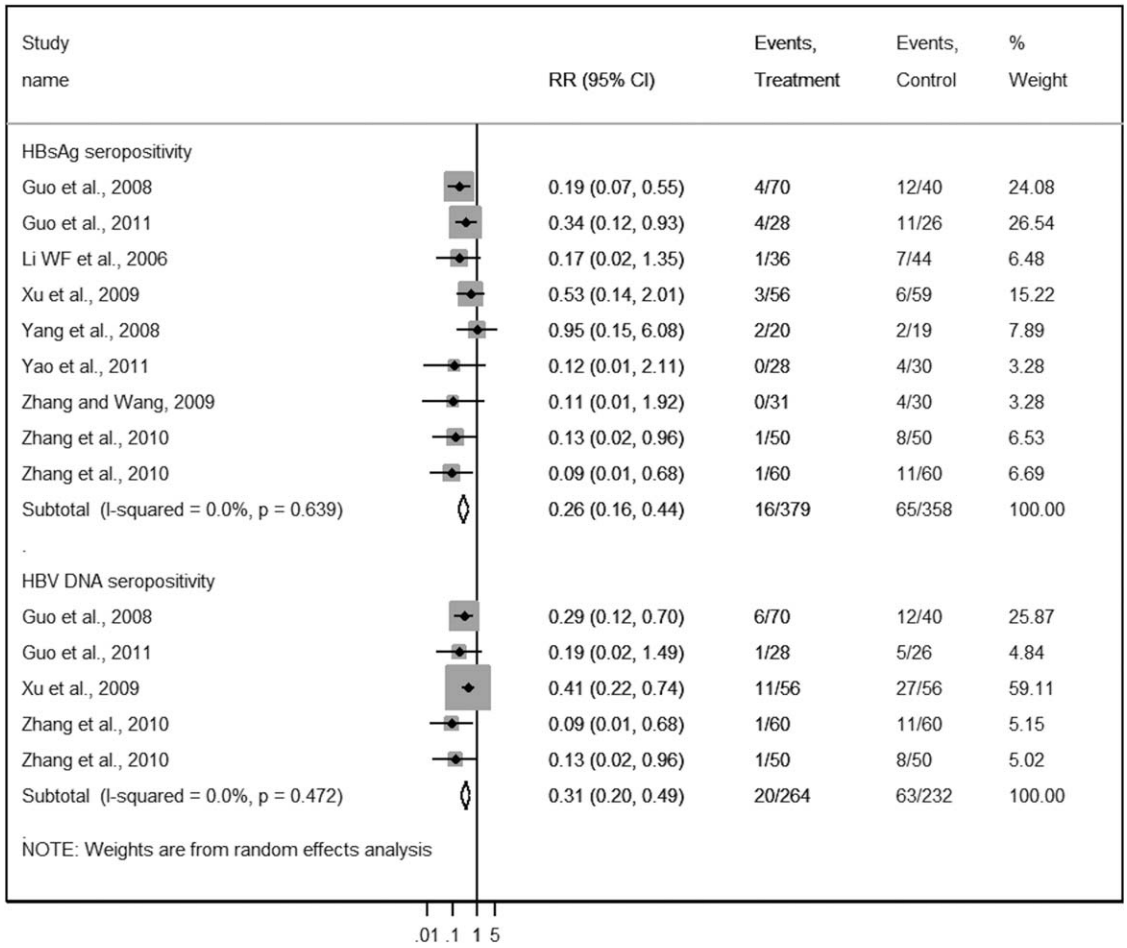

Fig. 2. Forest plots of infant outcomes for RCTs comparing any antiviral therapy versus control at 6-12 months follow-up.

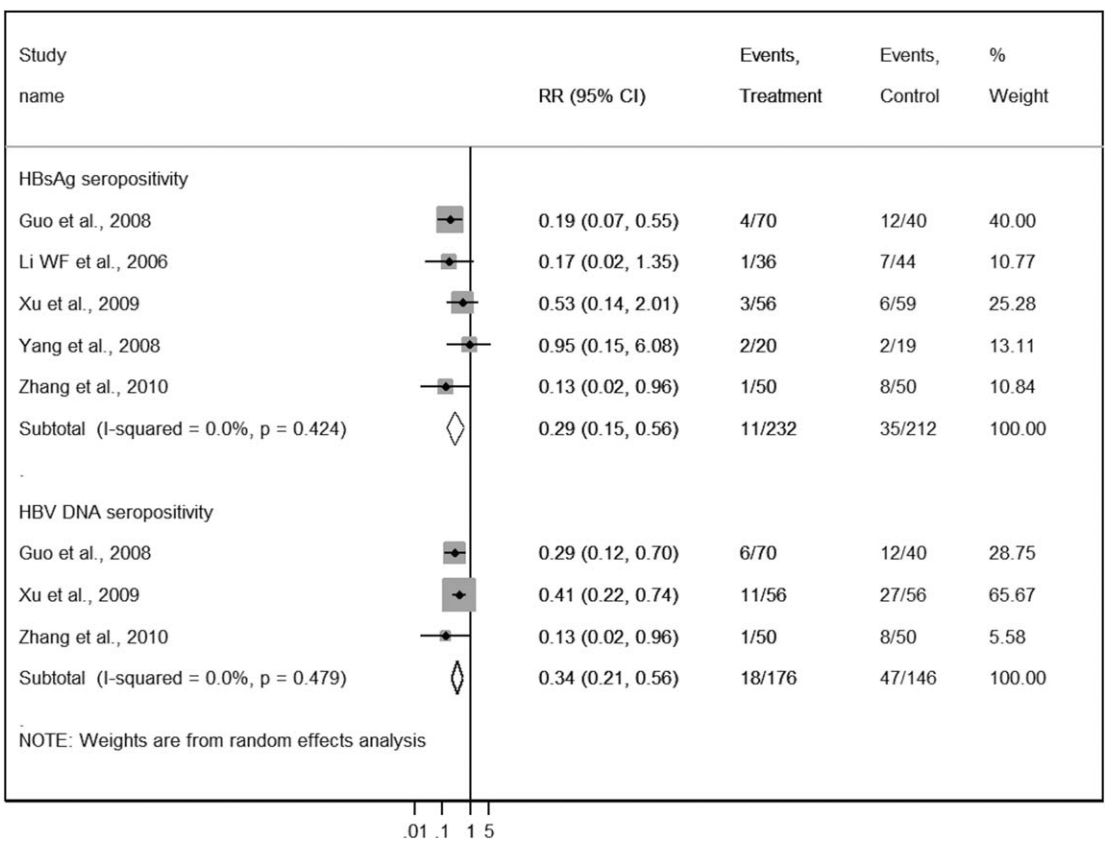

Fig. 3. Forest plots of infant outcomes for RCTs comparing lamivudine versus control at 6-12 months follow-up.

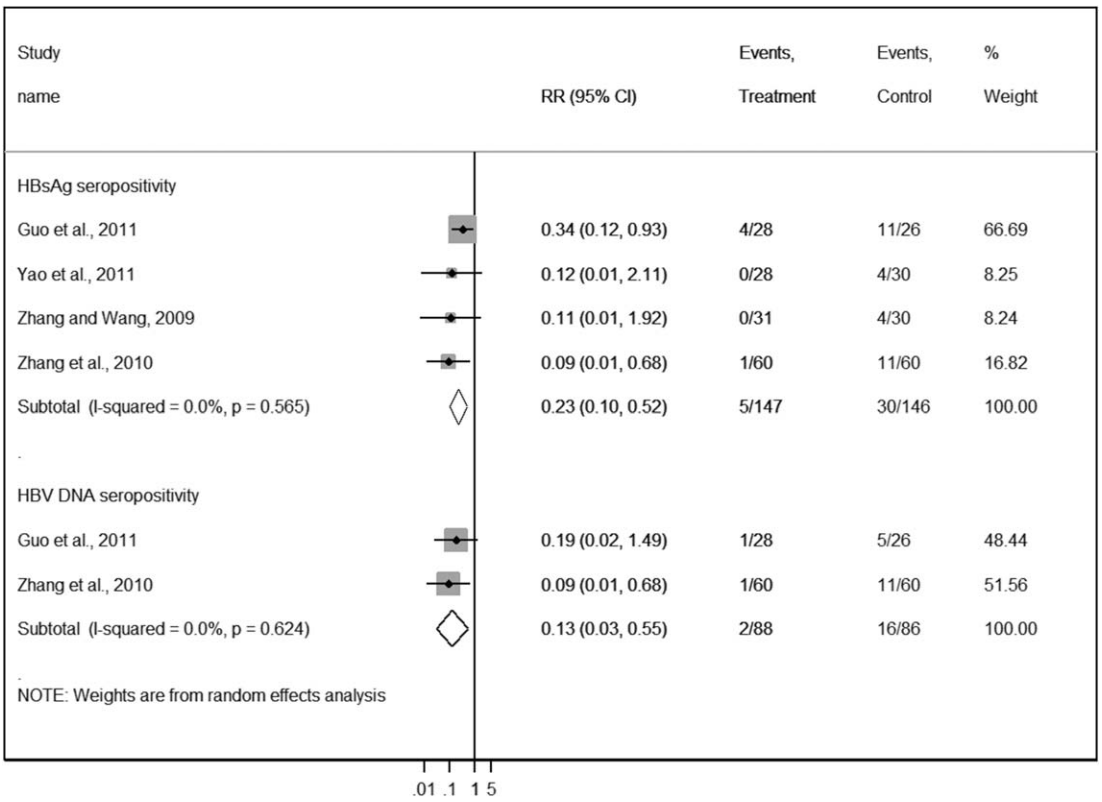

Fig. 4. Forest plots of infant outcomes for RCTs comparing telbivudine versus control at 6-12 months follow-up.

(one cohort, RR = 1.6, 95% CI 1.2-2.2), and at 28 weeks postpartum (one cohort, RR = 1.7, 95% CI 1.2-2.29). Tenofovir compared to control showed significant improvement in HBV DNA suppression at delivery (two cohorts, RR = 45.4, 95% CI 9.3-222.5) but not ALT normalization or HBeAg seroconversion.

Compared to lamivudine, pregnant women treated with telbivudine had significantly greater HBV DNA

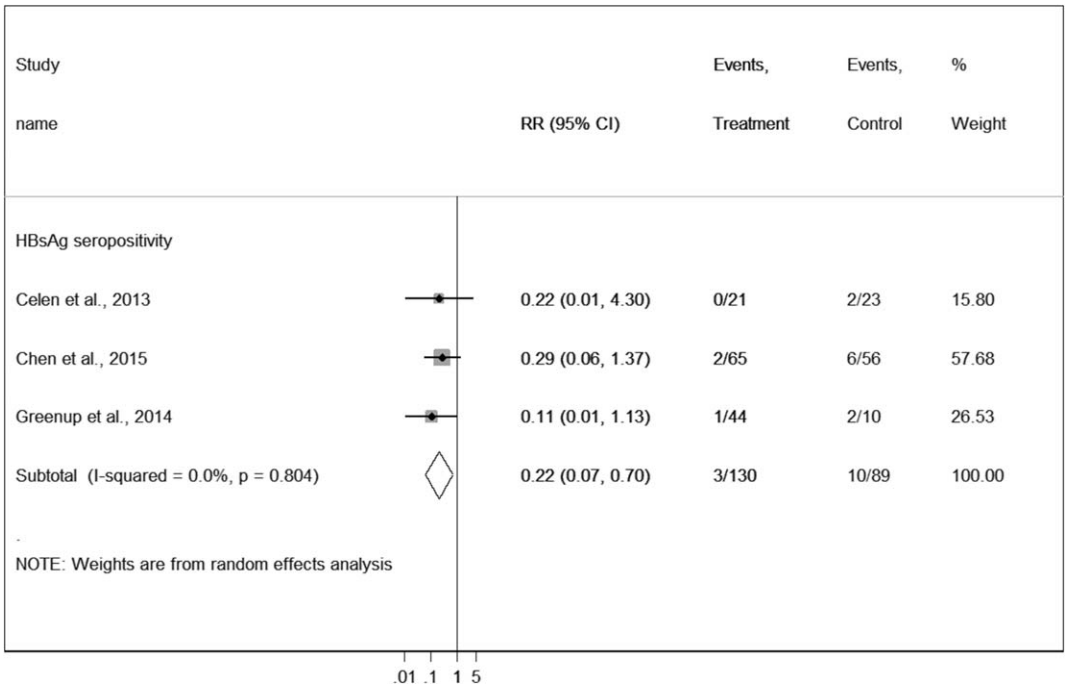

Fig. 5. Forest plots of infant outcomes for non-RCTs comparing tenofovir versus control at 6-12 months follow-up.

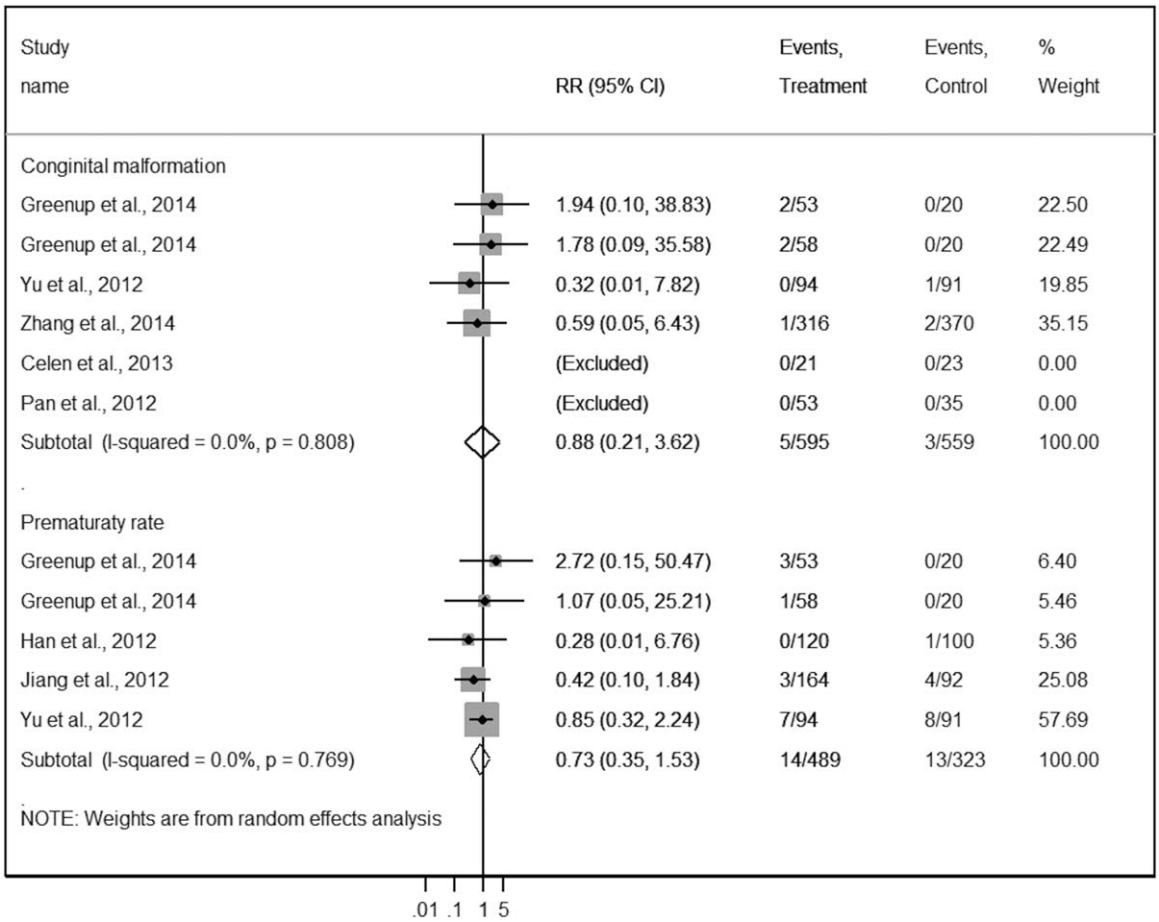

Fig. 6. Forest plot of congenital malformation and prematurity rates reported for studies comparing any antiviral therapy versus control.

suppression at delivery (one cohort, RR = 1.8, 95% CI 1.3-2.6) but not HBeAg loss (RR = 1.1, 95% CI 0.1-21.5) or seroconversion (RR = 0.6, 95% CI 0.03-15.2).

When comparing any antiviral therapy versus control for maternal harms, no statistically significant difference was found in postpartum hemorrhage rate, cesarean section rate, and elevated creatine kinase rate. The quality of the evidence in maternal outcomes was very low due to the observational nature of the studies, imprecision, and indirectness. Figures 7–9 show maternal outcomes reported at delivery in studies comparing lamivudine, telbivudine, and tenofovir treatment versus control group, respectively. Supporting Table 2 summarizes the quality of evidence (Grading of Recommendations Assessment, Development, and Evaluation) for infant and maternal outcomes.

Publication Bias. We were unable to evaluate publication bias due to the small number of studies for each outcome.

Discussion

For women who are or may become pregnant, consideration of the potential harms and benefits to the fetus as well as the mother complicates medication treatment decisions, such as administering antiviral therapy for CHB during pregnancy. Although the benefit for antiviral therapy is unproven for the many women of childbearing age who are in the immune tolerant phase of CHB, these women have the highest risk of MTCT. Thus, characterizing the safety of these medications for the mother and fetus during pregnancy can help inform potential treatment choices for women of childbearing age. Even for women who are in the immune active phase of CHB infection antiviral treatment may be postponed until after completion of childbearing as long as they have compensated liver disease. Additionally, postdelivery neonatal combined immunoprophylaxis successfully prevents HBV infection in approximately 90% of infants. Thus, prevention of MTCT of HBV does not necessarily mandate antiviral treatment during pregnancy for most women. However, the current failure rate of postexposure neonatal immunoprophylaxis against MTCT of HBV may be unacceptably high (~9%) in women with high levels of viremia (serum HBV DNA $>10^6$ copies/mL; $\sim 2 \times 10^5$ IU/mL).[10]

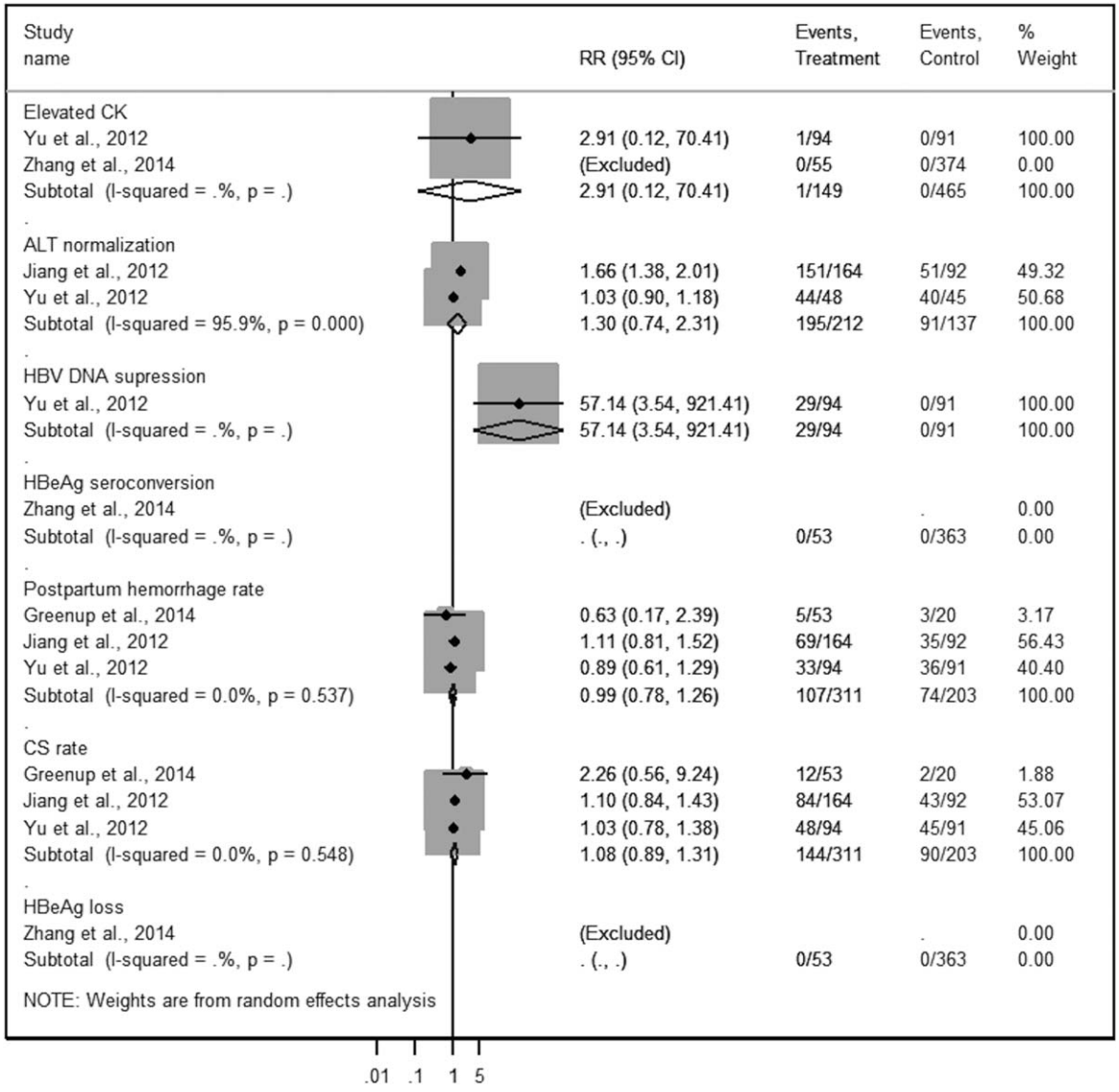

Fig. 7. Forest plot of maternal outcomes for non-RCTs comparing lamivudine versus control at delivery.

Among infants who received hepatitis B vaccine starting at birth, this meta-analysis found that antiviral therapy with lamivudine, telbivudine, or tenofovir in pregnant women with high levels of HBV DNA reduced MTCT rates, with over 70% reductions in the rates of infant HBsAg and HBV DNA positivity at 6-12 months postpartum. In non-head-to-head trials, telbivudine showed higher rates of HBV DNA suppression, ALT normalization, and HBeAg seroconversion than lamivudine. For tenofovir, there were insufficient controlled outcome data. No safety issues for maternal or fetal outcomes were identified in our meta-analysis of these studies. Thus, antiviral therapy in the third trimester for women who are HBeAg-positive with an HBV DNA level greater than 2×10^5 IU/mL to prevent MTCT seems warranted (see the accompanying AASLD Hepatitis B Treatment Guidelines for details).

Although lamivudine, telbivudine, and tenofovir are licensed for CHB and HIV treatment, none of these drugs are approved for use in pregnancy. Telbivudine and tenofovir are currently rated pregnancy category B, and lamivudine pregnancy category C, by the US Food and Drug Administration based primarily on animal data, with no clear evidence of harm in sparse human data. However, the substantial experience in the use tenofovir and lamivudine in HIV-infected pregnant women to prevent HIV transmission has not identified any significant safety concerns for either mother or newborn.[20] Recent data in women with HIV have reported lower bone mineral content in newborns exposed to tenofovir throughout pregnancy[52]; but earlier data did not show any impact on early growth in infants exposed to tenofovir *in utero*,[53] so the significance of this finding is unclear. Additionally, initiating tenofovir, lamivudine, or

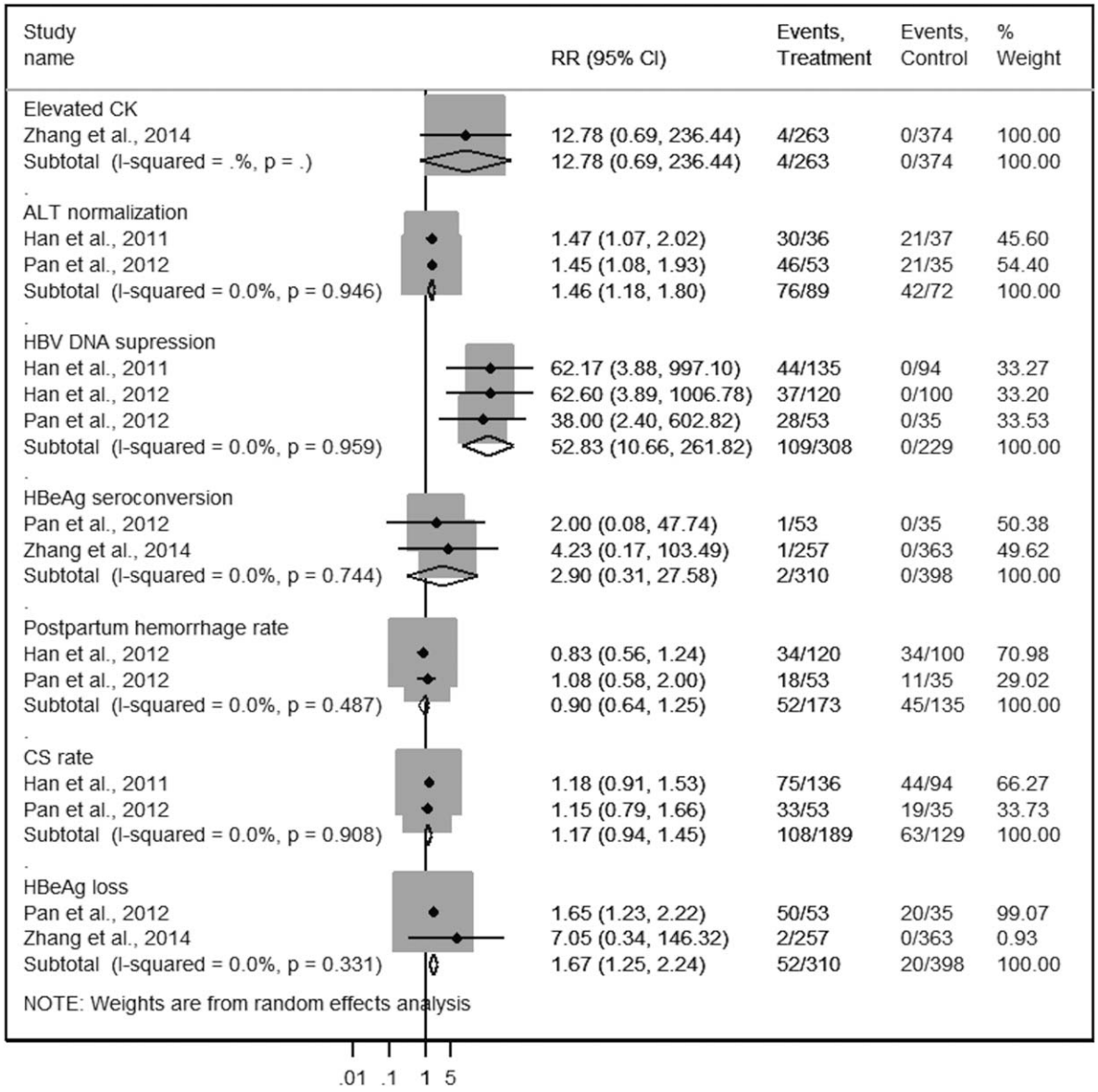

Fig. 8. Forest plot of maternal outcomes for non-RCTs comparing telbivudine versus control at delivery.

telbivudine for CHB during pregnancy may be less worrisome because the antiviral agents are usually started in the late second or early third trimester in mothers with high HBV DNA levels, to reduce maternal viremia and hence the risk of MTCT of HBV. Concern remains over the propensity to develop viral resistance to lamivudine or telbivudine[54] if it is used throughout the pregnancy or postpartum, rather than restricted to the late second or third trimester. On the other hand, tenofovir has a high resistance barrier with no resistance identified to date after up to 6 years of monotherapy for CHB.[55]

The major limitation of this systematic review is the absence of studies warranting high confidence. With a paucity of RCTs, most of the data are derived from cohort studies, which are subject to significant biases, especially selection bias. Additionally, despite a report from the Antiretroviral Pregnancy Registry finding no increased risk of birth defects for lamivudine or tenofovir,[25] data on fetal safety with antivirals remain limited, particularly for telbivudine. Recommendations for management of chronic HBV infection during pregnancy are provided in the updated AASLD guidelines.[56]

In conclusion, in pregnant women with chronic HBV infection, the oral antiviral therapies lamivudine, telbivudine, and tenofovir lower HBV DNA levels as they do in nonpregnant women and reduce the rates of MTCT. These effects were demonstrated in women who are HBeAg-positive with high viral loads ($>10^6$ copies or $\sim 2 \times 10^5$ IU/mL). The limited safety data suggest no increased risk of adverse maternal or fetal

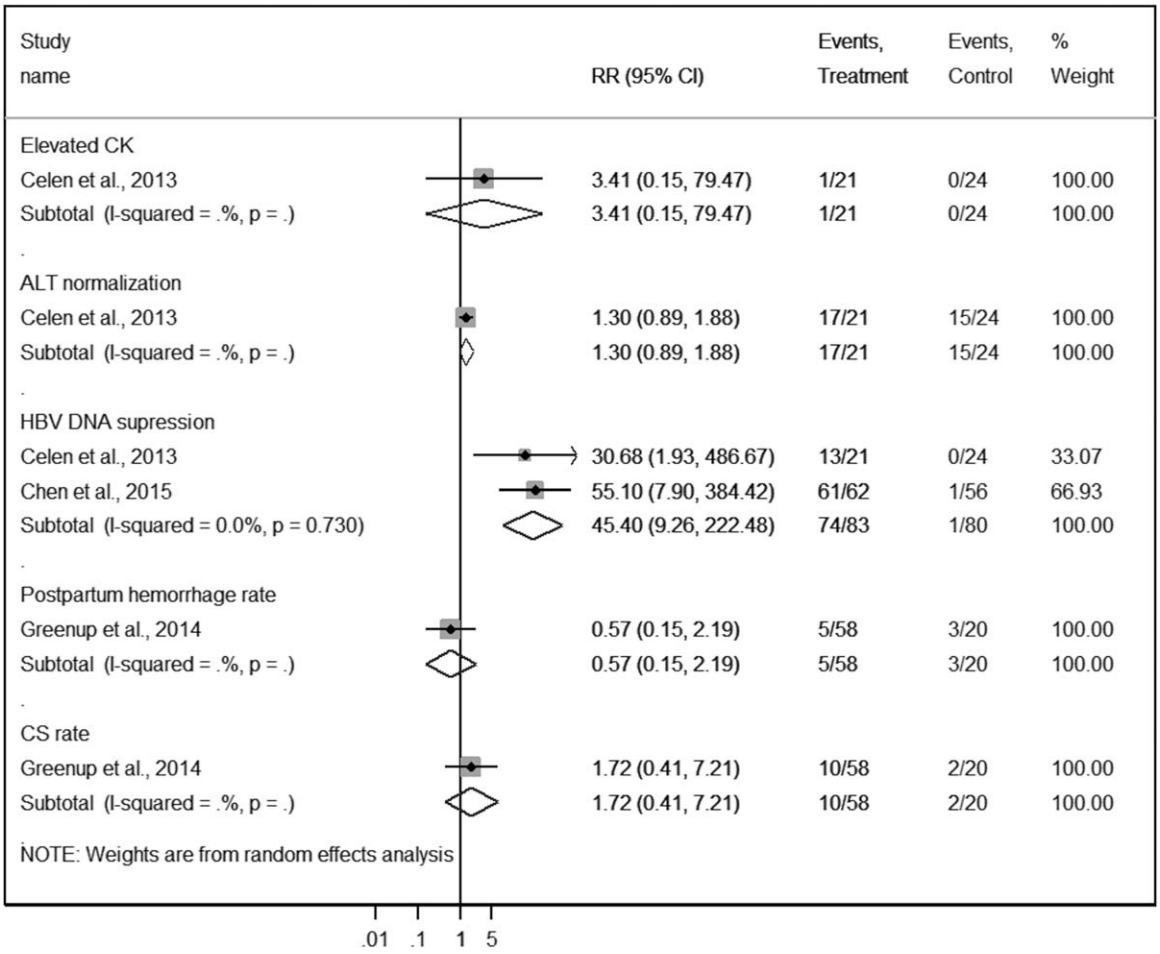

Fig. 9. Forest plot of maternal outcomes for non-RCTs comparing tenofovir versus control at delivery.

outcomes. Larger-scale RCTs of tenofovir are ongoing, and these results are eagerly awaited. In the meantime, the use of these agents in women who are HBeAg-positive and have HBV DNA $>10^6$ copies/mL (200,000 IU/mL) in the third trimester to prevent MTCT is recommended.

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