Original Article

Comparing the Efficacy and Safety of Treating Chronic Hepatitis B Infection during Pregnancy with Lamivudine, Telbivudine, and Tenofovir: A Meta-analysis

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Abstract

Background and Aims: The perinatal transmission of hepatitis B virus (HBV) remains an important global health problem. Here, a systematic review and meta-analysis were conducted to evaluate the evidence regarding the efficacy and maternal/fetal safety of treating pregnant women with lamivudine, telbivudine (LdT), and tenofovir (TDF). ***Methods:*** A PubMed and Scopus search resulted in 1,076 records, which were reduced to 36, containing 7,717 pregnant women with chronic HBV infection and 7467 infants meeting the inclusion criteria. The latest search was in August 2019. ***Results:*** Treatment with LdT, but not lamivudine and TDF, could significantly reduce the hepatitis B virus surface antigen-positive rate (odds ratio (OR) = 0.37) in infants; it also led to higher rates of hepatitis B e antigen loss (OR = 12.14), hepatitis B e antigen seroconversion (OR = 8.93), and alanine aminotransferase normalization in mothers (OR = 1.49). Each of these treatments was able to significantly reduce HBV DNA positivity at birth (total OR = 0.19) and mother-to-child-transmission of HBV (total OR = 0.15), and to cause higher rates of HBV DNA suppression in mothers (total OR = 25.53). However, nucleos(t)ide analogues might also be involved in creatine kinase elevation (total OR = 7.48). In contrast, no significant association was found between nucleos(t)ide analogue therapy and preterm/premature births, congenital malformation, low birth weight, and abortion or fetal/infant death. The results suggested LdT's high capability of preventing mother-to-child-transmission. However, TDF failed to show significant associations to a reduced risk of mother-to-child-transmission, probably due to the low number of patients included. ***Conclusions:*** Although using either lamivudine, LdT, or TDF could lead to more favorable maternal/fetal outcomes, LdT seemed to show more potential in resolving certain infant- and maternal-related outcomes. More studies on the safety profile of such treatments are required.

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Introduction

Approximately 240 million people are chronically infected with hepatitis B virus (HBV), which has a high rate of mortality annually.[1] During recent decades, the epidemiology of HBV infection had decreased, due to the impact of universal infant vaccination programs. HBV vaccination is an effective and safe approach, given on day 0 and at the end of 1 month and 6 months.[2] However, this method is ineffective for patients already infected with HBV.

HBV can be acquired by contaminated blood product exposure, sexual activity, and perinatal transmission. Perinatal transmission, or mother-to-child transmission (MTCT), remains a critical infection route in hepatitis B-endemic countries. Regardless of the fact that pegylated-interferon alpha-2a can lead to high rates of hepatitis B virus surface antigen (HBsAg) loss,[3] nucleos(t)ide analogues (NAs), including lamivudine (LAM), telbivudine (LdT), entecavir, adefovir and tenofovir (TDF), are unable to eradicate this chronic infection. However, they seem to be able to decrease the risk of MTCT. Without prophylaxis, in mothers who are positive for both HBsAg and hepatitis B e antigen (HBeAg), the risk for transmission to the baby is high.[4] In a considerable

Keywords: Hepatitis B virus; Antiviral therapy; Tenofovir; Telbivudine; Lamivudine; Nucleos(t)ide analogues; Pregnancy.

Abbreviations: CHB, chronic HBV infection; CI, confidence interval; CK, creatine kinase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; LAM, lamivudine; LdT, telbivudine; MTCT, mother-to-child-transmission; NA, nucleos(t)ide analogue; TDF, tenofovir.

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number of newborn infants from mothers with chronic HBV infection (CHB) infection, HBsAg and/or HBV DNA detection is positive, which may either take months to clear after birth or even become chronic.[5–9]

The majority of data regarding the safety and efficacy of anti-HBV therapies have been derived from studies conducted on human immunodeficiency virus (HIV)-positive mothers.[10,11] However, during recent years, an increasing number of studies have focused on assessing the safety and efficacy of antiviral agents in pregnancy for HBV-infected women and their infants. Because of a wide number of studies that have reported the efficacy and safety of antiviral therapy via different types of approved NAs, and their widely different results, it is important to conduct an up-to-date analysis of these studies. Thus, we conducted a systematical review and meta-analysis to reveal the most potent and safest drugs, as well as to evaluate the risks and benefits associated with NAs therapy in pregnant women with CHB.

Although other comprehensive systematic reviews and meta-analyses have been conducted, the results needed to be updated and to cover various different aspects of NAs therapy during pregnancy. For example, Brown *et al.*[12] performed a systematic review and meta-analysis comparing the effect of oral HBV therapy on different infant and maternal outcomes. However, that study was carried out years ago and may need to be updated, based on recently published studies. A more recent attempt by Hyun *et al.*[13] conducted a meta-analysis containing 10 studies (733 women) on the efficacy and safety of TDF. Those investigators found it a safe and tolerable drug for both the mother and fetus. Comparing the efficacy and safety of LAM, LdT, and TDF with the latest reported studies may be beneficial in revising current findings on the management of HBV-infected mothers during their pregnancies.

Methods

Publication search

A systematic literature search was conducted for all published articles associated with NAs therapy for CHB during pregnancy, using the PubMed and Scopus databases, with no limitation period. The last search update was on August 1, 2019. Selected keywords covered all studies associated with LAM, LdT, and TDF therapies for CHB during pregnancy. The keywords employed were ((Tenofovir) OR (Telbivudine) OR (Adefovir) OR (Entecavir) OR (Lamivudine) OR (Nucleoside analogues) OR (Nucleotide analogues) OR (Nucleos(t)ide analogues)) AND ((Hepatitis B virus) OR (HBV)) AND ((Pregnancy) OR (Pregnant) OR (Intrauterine transmission) OR (Perinatal transmission) OR (Utero transmission) OR (Vertical transmission)). The references for the selected articles were also checked for any articles missed.

Selection criteria

Among the studies found, only controlled or comparative studies that enrolled pregnant women diagnosed with CHB infection (a persistence of HBsAg for more than 6 months), who received LAM, LdT, or TDF were considered for analysis. As the current recommendation of NAs treatment for MTCT had been suggested to be initiated from week 24 of pregnancy, studies that contained only patients treated before week 24 were excluded. The studies needed to include essential information, such as the type of treatment(s) and recorded outcomes during the pregnancy and/or delivery, as well as infant outcomes. All the studies included had to compare the results with control groups, which could be defined as pregnant women who did not receive any type of oral HBV therapy during the pregnancy. However, their infants may have been treated with hepatitis B immune globulin and/or vaccine. Only studies in English were considered. Moreover, studies of patients coinfected with hepatitis C, hepatitis D, or human immunodeficiency virus were excluded, to minimize the effects of other diseases in the outcomes of treatments. In addition to the original articles, review studies and meta-analyses were searched for probable missing reports and studies.

Data extraction

Data extraction was performed from each article by two authors, independently. All the extracted data, including patient characteristics, treatment protocols, as well as maternal and infant outcomes, were carefully reviewed and categorized before discussion. The final extended data were rechecked with caution, compared, and inconsistencies resolved by referring to the full text of the articles.

Outcomes

Both maternal and infant outcomes were considered and analyzed. Infant outcomes, including the risk of MTCT, HBV DNA and HBsAg positivity at birth and at the age of 6–12 months, congenital malformation, low birth weight rate, premature/preterm birth rate, abortion rate, and infant/fetus fetal rate were considered. MTCT was defined by HBsAg seropositivity and/or HBV DNA positivity at 6–12 months. Moreover, maternal outcomes were also taken into account, including HBV DNA suppression, alanine aminotransferase normalization, HBeAg loss/seroconversion, postpartum hemorrhage rate, and elevated creatine kinase (CK).

Statistical analysis

Statistical analyses were carried out using Review Manager statistical software, version 5.3. Dichotomous data were expressed as odds ratio (OR) and 95% confidence intervals (CIs). Mantel–Haenszel was used. Otherwise, the meta-analysis was conducted using a fixed-effect model.[14] Specifically, the analysis was performed with the use of a random-effects model (Mantel–Haenszel) after exploring for causes of heterogeneity or the fixed-effects models. Cochran Q test and the I^2 statistic were used for examining heterogeneity among studies and were considered significant if p <0.10 or I^2 >50%. When significant heterogeneity in the results was observed, the random effect model was employed. However, in homogeneous conditions, the fixed-effect model was used. During the entire study, a p-value of <0.05 was considered as statistically significant for all outcomes.

Results

The initial search resulted in 1,076 records. Before starting the primary screening, duplicate records, and non-English articles were identified and excluded (n = 269). Checking titles of the articles led to the omission of 529 records. The remaining studies (n = 278) were evaluated by reviewing

their abstracts. As a result, 173 studies were identified as nonrelevant records. Finally, the full text of 105 studies was checked to select those matching the inclusion criteria. Seventy articles were excluded, due to different reasons (lack of original data, not containing control group, insufficient data, acute HBV, combination therapy, treatment initiation in the first trimester, and case report), while one new study was included which had not appeared among the original search results. Eventually, 36 studies were included for meta-analysis. The study selection process and reasons for exclusions are presented in Fig. 1.

Studies' selection and characteristics

Thirty-six studies, containing 7,717 pregnant women (4,468 treated; 3,249 untreated) with CHB and 7,467 infants (4,317 from treated mothers; 3,150 from untreated mothers), were included. From these studies, there were 15 groups treated with LAM, 17 groups treated with LdT,[4,6–9,15–26] and 12 groups treated with TDF.[16,24,26–35] Some of them covered more than one NA (n = 7).[7,15,16,24,26,28,31] Contrary to relatively older studies, the majority of recent studies did not cover LAM. In all studies for the group under treatment, antiviral therapy was initiated in the second or third trimester, while discontinuance occurred at different times. All the studies presented original data associated with the control group, except for one, where the control group was taken from documented patient data in the literature.[36] Table 1 summarizes the characteristics of the studies.

Infant outcomes

Comparison of antiviral therapy with no treatment: Results adapted from 25 studies in the analysis revealed that NA (LAM, LdT, and TDF) therapies could significantly reduce the rate of HBsAg positivity at birth for infants born from CHB mothers (OR [95% CIs] = 0.50 [0.38, 0.67]; I^2 = 61%; p-value <0.00001) (Fig. 2). As the results of treating CHB-positive pregnant women with these drugs, the risk of birth of an infant with positive HBV DNA was also reduced significantly (OR [95% CIs] = 0.19 [0.10, 0.36], I^2 = 84%, p-value <0.00001) (Fig. 3). The rate of MTCT for any separated drug was extractable in almost all studies included. Reports were analyzed from a total of 3,629 newborn infants from CHB mothers and 3,245 controls, who had received hepatitis B immune globulin and vaccine, and also were followed for more than 6 months. Results from the 36 studies revealed that starting antiviral therapy in the second or third trimester could significantly protect infants from CHB (OR [95% CIs] = 0.15 [0.11, 0.19], I^2 = 12%, p-value <0.00001) (Fig. 4).

Following analysis of the risk of congenital malformation in a total of 1,954 born babies from CHB mothers and 2,194 controls, no statistical difference was obtained. However, those who were exposed to NA therapy seemed to be more

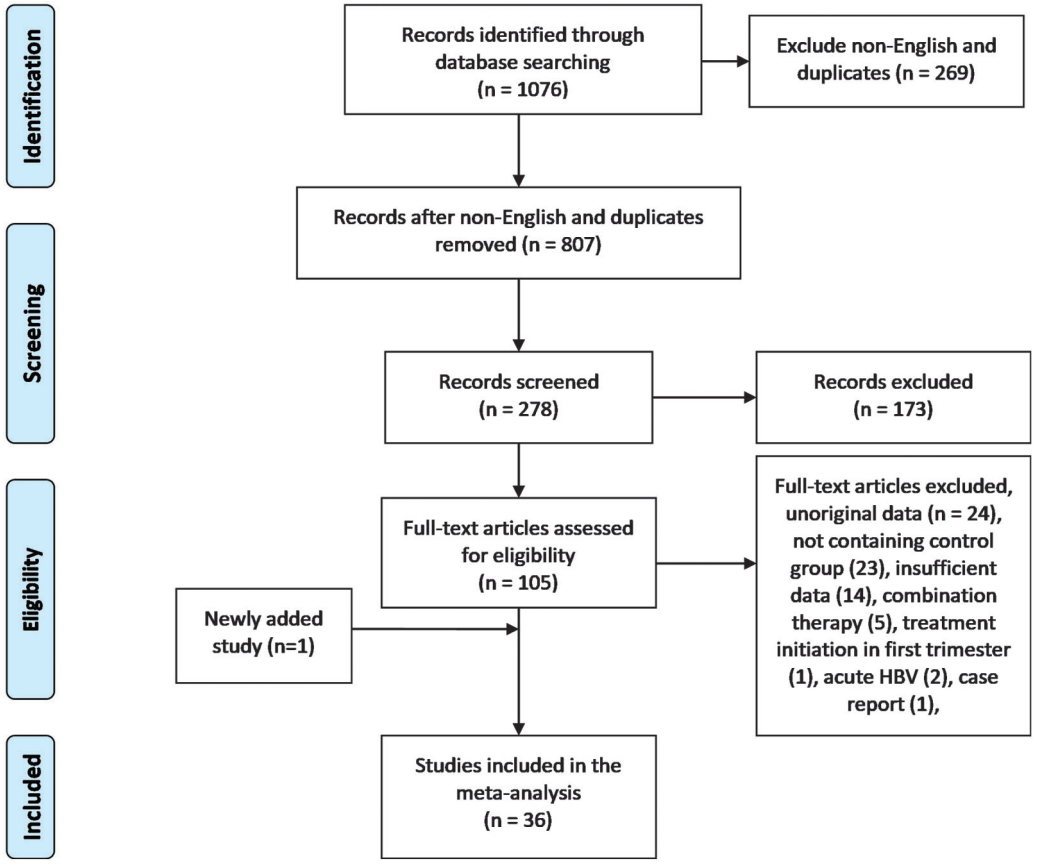

Fig. 1. The study selection process.

Table 1. Characteristics of the included studies

Author, year	Region	Participants, mothers: infants	Interventions, mothers	Hepatitis B immune globulin and vaccine[#]	Maternal age in years	Baseline HBV DNA level, Log10 IU/mL	Baseline alanine aminotransferase, U/L	Treatment start, gestational week	Treatment discontinuation. postpartum week	Duration up to delivery, week	Study design
Li, 2003[40]	China	43:43	Lamivudine	N/A	N/A	7.49 ± 0.54	N/A	28	4	12	RCT
		52:52	Control		N/A	7.05 ± 1.29					
Zonneveld, 2003[41]		Netherlands	8:8			Lamivudine	Yes	21.25 ± 2.65	9.30	32.4 ± 16.3	34
			At delivery	6	Cohort study						
24:25	Control		23 (16–34)	9.39		N/A					
Su, 2004[36]	China	38:12	Lamivudine	Yes	N/A	N/A	N/A	N/A	N/A	N/A	Cohort study
		10:10	Control		N/A	N/A	N/A				
Ni, 2005[42]	Taiwan	29:29	Lamivudine	N/A	14.7 ± 5.6	10.95	214 ± 195	N/A	N/A	N/A	Prospective, open-label, nonrandom
		29:29	Control		14.0 ± 5.8	9.32	165 ± 123				
Xu, 2009[5]	United Kingdom	89:56	Lamivudine	Yes	26 (19–32)	2220.0 ± 1610.9 MEq/mL*	0.4 (0.1–5.3) × ULN	32	4	8	RCT
		61:59	Control		25 (20–36)	2692.7 ± 1627.0 MEq/mL*	0.4 (0.1–6) × ULN				
Han, 2011[6]	China	135:132	Telbivudine	Yes	27 (20–38)	8.10 ± 0.56	35.7 ± 43	20–32	4	8–20	Cohort study
		94:94	Control		26 (20–35)	7.98 ± 0.61	42.5 ± 40.1				
Yu, 2011[43]	China	94:94	Lamivudine	Yes	27.68 ± 3.65	6.97 ± 1.95	394.36 ± 372.18	24–32	After childbirth, till satisfactory efficacy or drug resistance mutation appeared	8–16	Cohort study
		91:91	Control		26.33 ± 3.24	7.20 ± 0.94	294.03 ± 233.83				
Yu, 2012[44]	China	94:94	Lamivudine	Yes	26.64 ± 4.17	7.63 ± 0.54	≥40	24–32	Variable after delivery	8–16	Cohort study
		91:91	Control		25.78 ± 3.89	7.71 ± 0.71	45.0				
Pan, 2012[4]	China	53:54	Telbivudine	Yes	27 (21–34)	8.08 (rage 6.6–9.4)	60.40 (41.40–422.00)	Second trimester	Variable after delivery	12–27	Cohort study
		35:35	Control		27 (21–33)	8.08 (range 6.76–9.08)	63.20 (42.40–262.50)				
Celen, 2013[27]	Turkey	21:21	Tenofovir	Yes	28.2 ± 4.1	>7	56 (22–71)	18–27	4	13–22	Retrospective study
		24:23	Control		26.9 ± 2.9	>7	52 (19–77)				

(*continued*)

Table 1. (*continued*)

Author, year	Region	Participants, mothers: infants	Interventions, mothers	Hepatitis B immune globulin and vaccine[#]	Maternal age in years	Baseline HBV DNA level, Log10 IU/mL	Baseline alanine aminotransferase, U/L	Treatment start, gestational week	Treatment discontinuation. postpartum week	Duration up to delivery, week	Study design
Zhang, 2014[7]	China	55:54	Lamivudine	Yes	28.42 ± 7.11	7.62 ± 0.37	39.65 ± 26.37	28–30	4	10–12	Prospective, open-label, nonrandom
		374:370	Control		28.97 ± 64.59	7.58 ± 0.45	29.53 ± 20.72				
Zhang, 2014[7]	China	263:262	Telbivudine	Yes	29.78 ± 6.31	7.69 ± 0.44	30.06 ± 28.86	28–30	4	10–12	Prospective, open-label, nonrandom
		374:370	Control		28.97 ± 4.59	7.58 ± 0.45	29.53 ± 20.72				
Ayres, 2014[45]	Australia	21:18	Lamivudine	Yes	N/A	>7	N/A	32	2	8	Cohort study
		5:3	Control								
Greenup, 2014[28]	Australia	58:43	Tenofovir	Yes	30 ± 8.5	7.9 ± 08	28 (22–36)	32	12	8	Cohort study
		20:10	Control		28 ± 5	8 ± 04	25 (17–31)				
Greenup, 2014[28]	Australia	52:44	Lamivudine	Yes	28 ± 5.3	7.7 ± 06	22 (18–30)	32	12	8	Cohort study
		20:10	Control		28 ± 5	8 ± 04	25 (17–31)				
Nguyen, 2014[15]	Australia	44:44	Telbivudine	N/A	29.1 ± 4.9	8.0	23.5 (20–31.3)	32	4	8	Cohort study
		14:14	Control		27.1 ± 4.0		25.5 (18–35)				
Nguyen, 2014[15]	Australia	43:43	Lamivudine	N/A	30.9 ± 4.5	8.0	29.0 (17.5–40.5)	32	2–12	8	Cohort study
		14:14	Control		27.1 ± 4.0		25.5 (18–35)				
Han, 2015[8]	China	362:365	Telbivudine	Yes	27 (20–38)	8 (6–9.1)	19.9 (5.2–513.5)	N/A	N/A	N/A	Prospective, open-labeled, nonrandom
		92:92	Control		26 (20–35)	7.93 (6–9.5)	26.55 (8.1–262.5)				
Chen, 2015[32]	Taiwan	62:65	Tenofovir	Yes	32.41 ± 3.12	8.25 ± 0.45	23.27 ± 36.2	30	4	10	Prospective, open-labeled, nonrandom
		56:56	Control		32.45 ± 3.2	8.24 ± 0.35	16.59 ± 14.43				
Tekin Koruk, 2015[16]	Turkey	29:20	Tenofovir	Yes	27.4 ± 4.7	N/A	N/A	22.2 ± 8.5 (1–36)	N/A	~18	Retrospective
		54:54	Control		28.7 ± 4.9	1.98 ± 2.21	26.7 ± 22.9				
Tekin Koruk, 2015[16]	Turkey	4:4	Lamivudine	Yes	28.8 ± 5.1	N/A	N/A	22.2 ± 8.5 (1–36)	N/A	~18	Retrospective
		54:54	Control		28.7 ± 4.9	1.98 ± 2.21	26.7 ± 22.9				
Tekin Koruk, 2015[16]	Turkey	31:36	Telbivudine	Yes		N/A	N/A	22.2 ± 8.5 (1–36)	N/A	~18	Retrospective
		54:54	Control		28.7 ± 4.9	1.98 ± 2.21	26.7 ± 22.9				

(*continued*)

Table 1. (*continued*)

Author, year	Region	Participants, mothers: infants	Interventions, mothers	Hepatitis B immune globulin and vaccine[#]	Maternal age in years	Baseline HBV DNA level, Log10 IU/mL	Baseline alanine aminotransferase, U/L	Treatment start, gestational week	Treatment discontinuation. postpartum week	Duration up to delivery, week	Study design
Wu, 2015[9]	China	279:280	Telbivudine	Yes	27 (17–38	7.26 ± 0.50	111 (45–282)	24–32	N/A	8–16	Cohort study
		171:130	Control		28 (18–40)	7.40 ± 0.65	134 (44–330)				
Liu, 2016[18]	China	A: 50:50 B: 32:32	Telbivudine	Yes	27.88 ± 3.73 28.31 ± 3.81	7.67 ± 0.79 7.46 ± 0.73	46.64 ± 58.74 28.91 ± 38.48	before the third trimester 28–32	4	N/A 8–12	Cohort study
		78:78	Control		27.46 ± 3.47	7.56 ± 0.57	30.87 ± 28.99				
Pan, 2016[29]	China	97:95	Tenofovir	Yes	27.4 ± 3.0	8.2 ± 0.5	23.0 ± 22.4	30–32	4	8–10	RCT
		100:88	Control		26.8 ± 3.0	8.0 ± 0.7	20.5 ± 15.4				
Samadi Kochaksaraei, 2016[30]	Canada	23:24	Tenofovir	Yes	30 (28–34)	7.7 (3.2–8.1)	30 (18–50)	28–32	12	8–12	Cohort study
		138:146	Control		32 (29–36)	2.3 (1.6–3.1)	17 (12–24)				
Tan, 2016[17]	China	A: 34:34 B: 135:137	Telbivudine	Yes	29 29	2 (1.82–6.99) 7.69 (6.05–8.98)	A: 18 (9–500) B: 37 (6–697)	A: <14 B: 14–28	28	N/A 12–26	Cohort study
		316:320	Control		29	7.67 (6–8.91)	22 (5–623)				
Chen, 2017[22]	China	43:43	Telbivudine	Yes	28.1 ± 6.7	7.2 ± 0.7	89.3 ± 104.2	13–32	At delivery	8–27	Cohort study
		A: 79:79 B: 89:89	Control		A: 27.2 ± 5.5 B: 26.2 ± 4.5	A: 4.2 ± 0.8 B: 7.2 ± 0.6	A: 47.8 ± 57.9 B: 85.0 ± 86.3				
Hu, 2017[19]	China	149:128	Telbivudine	Yes	25.9 ± 3.7	7.43 ± 1.26	N/A	28–32	3–4	8–12	Cohort study
		179:156	Control		26.4 ± 3.4	7.37 ± 1.49	N/A				
Pan, 2017[46]	China	A: 66:66 B: 94:94	lamivudine	Yes	27.65 ± 4.08 27.37 ± 3.54	7.22 ± 0.61 7.26 ± 0.55	68.6 ± 103.6 36.4 ± 39.7	13–26 28–30	At delivery 12	14–27 10–12	Retrospective cohort
		89:89	Control		27.08 ± 4.22	7.33 ± 0.47	28.0 ± 35.4				

(*continued*)

Table 1. (*continued*)

Author, year	Region	Participants, mothers: infants	Interventions, mothers	Hepatitis B immune globulin and vaccine[#]	Maternal age in years	Baseline HBV DNA level, Log10 IU/mL	Baseline alanine aminotransferase, U/L	Treatment start, gestational week	Treatment discontinuation. postpartum week	Duration up to delivery, week	Study design
Sun, 2017[20]	China	A: 62:62 B: 61:61	Telbivudine	Yes	28.9 ± 11.8 29.7 ± 9.8	7.79 ± 0.22 7.75 ± 0.19	125.3 ± 57.6 132.3 ± 52.9	12 20–28	12	28 12–20	Cohort study
		65:65	Control		27.5 ± 12.9	7.74 ± 0.22	128.5 ± 48.7				
Wakano, 2017[31]	Japan	2:2	Tenofovir	Yes	28–37	9.0	N/A	28–32	4–8	8–12	Cohort study
		3:3	Control			9.0	N/A				
Wakano, 2017[31]	Japan	3:3	Lamivudine	Yes	28–37	9.0	N/A	28–32	4–8	8–12	Cohort study
		3:3	Control			9.0	N/A				
Yi, 2017[21]	China	A: 41:41 B: 179:179	Telbivudine	Yes	31.54 ± 4.21 27.77 ± 3.48	1.50 ± 0.62 8.05 ± 0.37	15.19 ± 8.53 21.58 ± 13.15	Third trimester	28	Up to 12	Cohort study
		176:176	Control		28.27 ± 3.65	7.94 ± 0.62	18.85 ± 9.83				
Chang, 2019[33]	Taiwan	110:115	Tenofovir	Yes	32.84 ± 3.57	8.25 ± 0.48	20.88 ± 28.94	30–32	Variable after delivery	8–10	Cohort study
		91:93	Control		32.69 ± 3.36	8.29 ± 0.49	19.10 ± 23.85				
Han, 2019[23]	China	139:137	Telbivudine	Yes	26 (20–43)	7.73 (6.04~9.30)	117 (56–1166)	12–34	Variable after delivery	6–28	prospective nonintervention study
		102:99	Control		26 (18–42)	7.72	(6.03~9.00)	164 (53–1025)			
Lin, 2018[35]	China	59:58	Tenofovir	Yes	28.31 ± 3.56	Not mentioned	54.62 ± 105.7	24	28	~16	Cohort study
		52:52	Control		28.06 ± 3.42	7.44 ± 0.80	57.5 ± 103.3				
Zeng, 2019[26]	China	A: 58:58 B: 51:51	A: Telbivudine B: Tenofovir	Yes	A:27.2 ± 10.8 B: 26.5 ± 9.5	A: 7.88 ± 0.65 B: 7.91 ± 0.75	A: 127.3 ± 72.2 B: 143.3 ± 104.6	20–28	12	N/A	Retrospective study
		36:36	Control		25.7 ± 10.9	7.69 ± 0.53	132.3 ± 78.3				
Jourdain, 2018[34]	China	168:147	Tenofovir	Yes	25.5 (22.6–29.1)	7.6 ± 1.5	N/A	28.3 (27.9–28.6)	8	N/A	RCT
		163:147	Control		26.7 (23.5–30.5)	7.3 ± 1.7		28.1 (27.9–28.6)			

(*continued*)

Table 1. (*continued*)

Author, year	Region	Participants, mothers: infants	Interventions, mothers	Hepatitis B immune globulin and vaccine[#]	Maternal age in years	Baseline HBV DNA level, Log10 IU/mL	Baseline alanine aminotransferase, U/L	Treatment start, gestational week	Treatment discontinuation. postpartum week	Duration up to delivery, week	Study design
Sheng, 2018[47]	China	91:79	Telbivudine	Yes	27.8 ± 4.17	8.15 ± 0.82	26.53 ± 8.32	24–32	12	8–16	Prospective open label multicenter study
		21:21	Control		26.8 ± 3.66	8.09 ± 1.04	23.62 ± 6.51				
Liu, 2019[24]	China	A: 396:400 B: 325:325	A: Telbivudine B: Tenofovir	Yes	A: 27.78 ± 3.56 B: 28.35 ± 4.35	A: 7.89 ± 0.66 B: 7.68 ± 0.70	A: 45.79 ± 66.34 B: 53.34 ± 71.87	22–28	12	12–18	Prospective, multicenter study
		136:136	Control		27.14 ± 4.72	7.71 ± 0.79	41.16 ± 62.46				
Foaud, 2019[48]	Egypt	34:34	Lamivudine	Yes	27 ± 2.9	3.9 103 (474–1.8 105)	N/A	Third trimester	12	~12	Prospective observation study
		39:39	Control		27.4 ± 4.6		N/A				

The control group in this Table represents the pregnant women who did not receive any type of oral hepatitis B virus therapy during the pregnancy. Their infants may be treated with hepatitis B immune globulin and/or vaccine.

Abbreviation: RCT, randomized controlled trial.

vulnerable to developing congenital malformation (OR [95% CIs] = 1.55 [0.80, 3.00], I^2 = 0%, *p*-value = 0.19). Regarding low birth weight, nine studies were available, which did not show a significant difference among the treated and untreated groups (OR [95% CIs] = 0.95 [0.57, 1.61], I^2 = 0%, *p*-value = 0.86). In order to evaluate the risk of NAs therapy threatening the life of a fetus/infant, abortion and fetal/infant death were analyzed separately. The results suggest a probable protective role of NAs therapy for each of these factors, but they were not significantly different among the treated and untreated patients (abortion: OR [95% CIs] = 0.47 [0.11, 1.92], I^2 = 31%, *p*-value = 0.29; fetal/infant death: OR [95% CIs] = 0.90 [0.54, 1.50], I^2 = 10%, *p*-value = 0.44).

There were 15 studies that compared premature/preterm birth rate among those who received NA, but significant associations were not found (OR [95% CIs] = 0.79 [0.58, 1.09], I^2 = 32%, *p*-value = 0.16).

Comparison of the results of LAM, LdT, and TDF: Following the use of LAM, LdT, and TDF, the risk of HBsAg positivity of an infant at birth was reduced compared with the cases not using any NAs; however, only LdT showed a significant result (LAM: OR [95% CIs] = 0.63 [0.38, 1.06], I^2 = 65%, *p*-value = 0.05; LdT: OR [95% CIs] = 0.37 [0.24, 0.57], I^2 = 67%, *p*-value <0.00001; TDF: OR [95% CIs] = 0.53 [0.21, 1.33], I^2 = 60%, *p*-value = 0.18) (Fig. 2). The results from 20 studies, containing 4,041 infants, demonstrated a significant reduction of HBV DNA positivity at birth in babies of CHB-infected mothers, who were exposed to each of the NAs (LAM: OR [95% CIs] = 0.15 [0.06, 0.40], I^2 = 23%, *p*-value = 0.0002; LdT: OR [95% CIs] = 0.23 [0.09, 0.57], I^2 = 88%, *p*-value = 0.001; TDF: OR [95% CIs] = 0.19 [0.11, 0.33], I^2 = 0%, *p*-value <0.00001) (Fig. 3).

The analysis implies a higher efficacy of LdT in reducing the risk of MTCT (OR [95% CIs] = 0.10 [0.06, 0.15], I^2 = 16%, *p*-value <0.00001). The next most effective is TDF (OR [95% CIs] = 0.17 [0.11, 0.27], I^2 = 0%, *p*-value <0.00001), then LAM (OR [95% CIs] = 0.24 [0.14, 0.39], I^2 = 11%, *p*-value <0.00001) (Fig. 4). When associated with the risk of congenital malformation, none of the NAs was higher than the others. Indeed, despite their nonsignificant differences, each of these drugs may be a risk factor for congenital malformation development (LAM: OR [95% CIs] = 1.33[0.38, 2.34], I^2 = 0%, *p*-value = 0.58; LdT: OR [95% CIs] = 1.70 [0.57, 5.03], I^2 = 0%, *p*-value = 0.34; TDF: OR [95% CIs] = 1.80 [0.43, 7.65], I^2 = 0%, *p*-value = 0.42).

Maternal outcomes

Comparison of antiviral therapy with no treatment: Among the selected studies, 10 (LAM = 3, LdT = 6, TDF = 1) evaluated the capacity of NAs therapy in terms of suppressing HBV DNA in mothers. The overall results showed encouraging results (OR [95% CIs] = 25.53 [8.59, 75.92], I^2 = 62%, *p*-value <0.00001) (Fig. 5A)). However, when HBeAg loss or seroconversion rates were analyzed, no significant differences were detected (HBeAg loss: OR [95% CIs] = 2.90 [1.58, 5.34], I^2 = 58%, *p*-value = 0.0006; HBeAg seroconversion: OR [95% CIs] = 2.68 [1.59, 4.52], I^2 = 53%, *p*-value = 0.0002). Moreover, no significant difference was found in the total results for the normalization of alanine aminotransferase levels (OR [95% CIs] = 1.37 [0.88, 2.14], I^2 = 95%, *p*-value = 0.17).

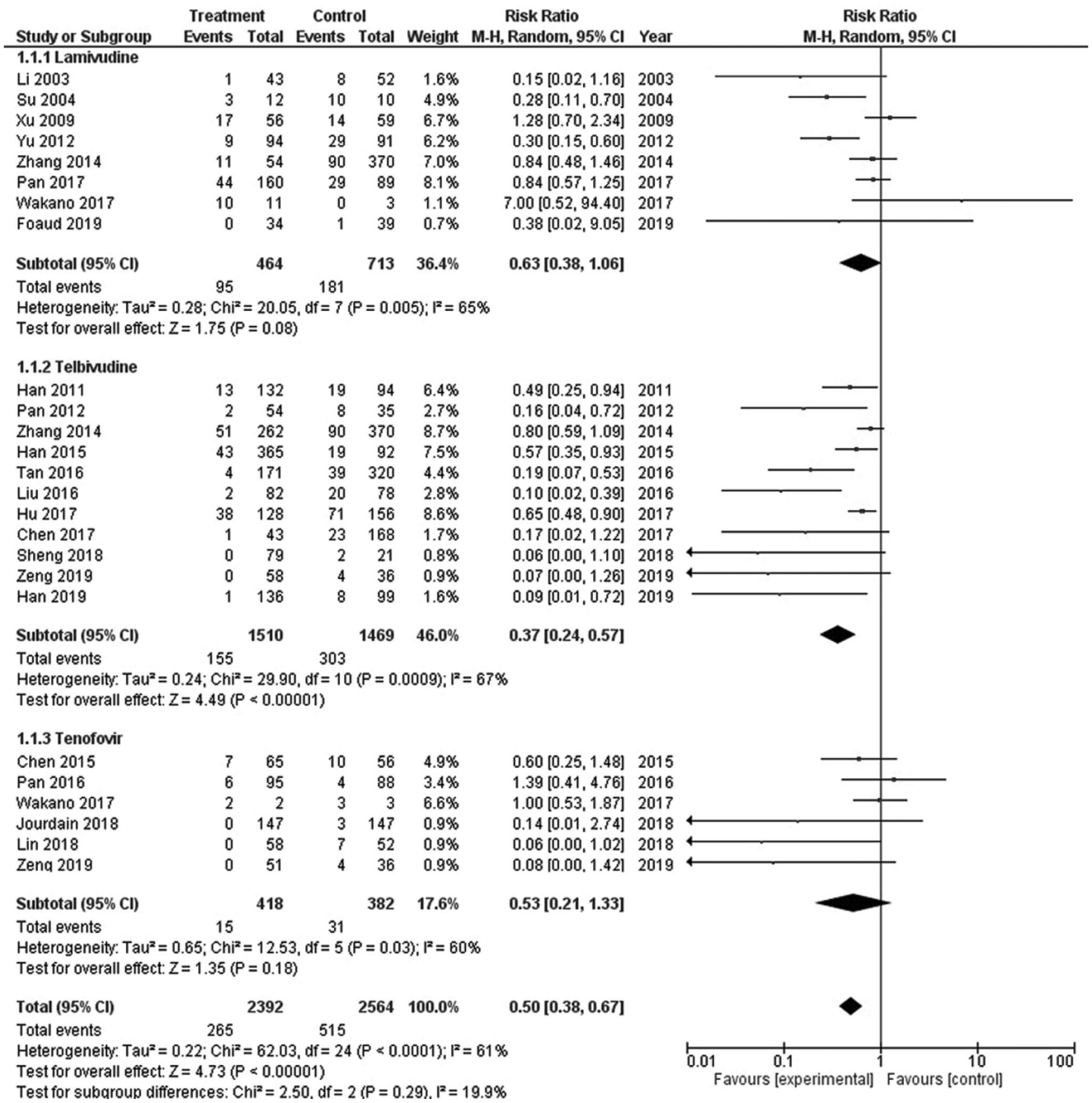

Fig. 2. Forest plots of infant HBsAg positivity at birth.

Abbreviation: HBsAg, hepatitis B surface antigen.

For maternal side effects, two parameters were considered: CK elevation and postpartum hemorrhage. Interestingly, among the 1,619 mothers monitored from the NAs group for CK elevation, 22 of them showed a high level of CK. In contrast, none of the 994 mothers without NA therapy was reported. This could suggest NAs playing a role in CK elevation during the pregnancy (OR [95% CIs] = 7.48 [2.41, 23.24], I^2 = 0%, *p*-value = 0.0005) (Fig. 5B). However, no significant differences were found among the NAs group and controls regarding postpartum hemorrhage (OR [95% CIs] = 0.94 [0.77, 1.14], I^2 = 0%, *p*-value = 0.52).

Comparison of LAM, LdT, and TDF: The calculations showed that LdT probably had a greater capacity to suppress HBV DNA in pregnant women, compared with LAM (LAM: OR [95% CIs] = 10.88 [0.61, 194.48], I^2 = 79%, *p*-value = 0.10; LdT: [95% CIs] = 61.15 [19.71, 189.74], I^2 = 0%, *p*-value <0.00001 (Fig. 5A)). Moreover, LdT was the only NA which was capable to induce HBeAg loss and seroconversion

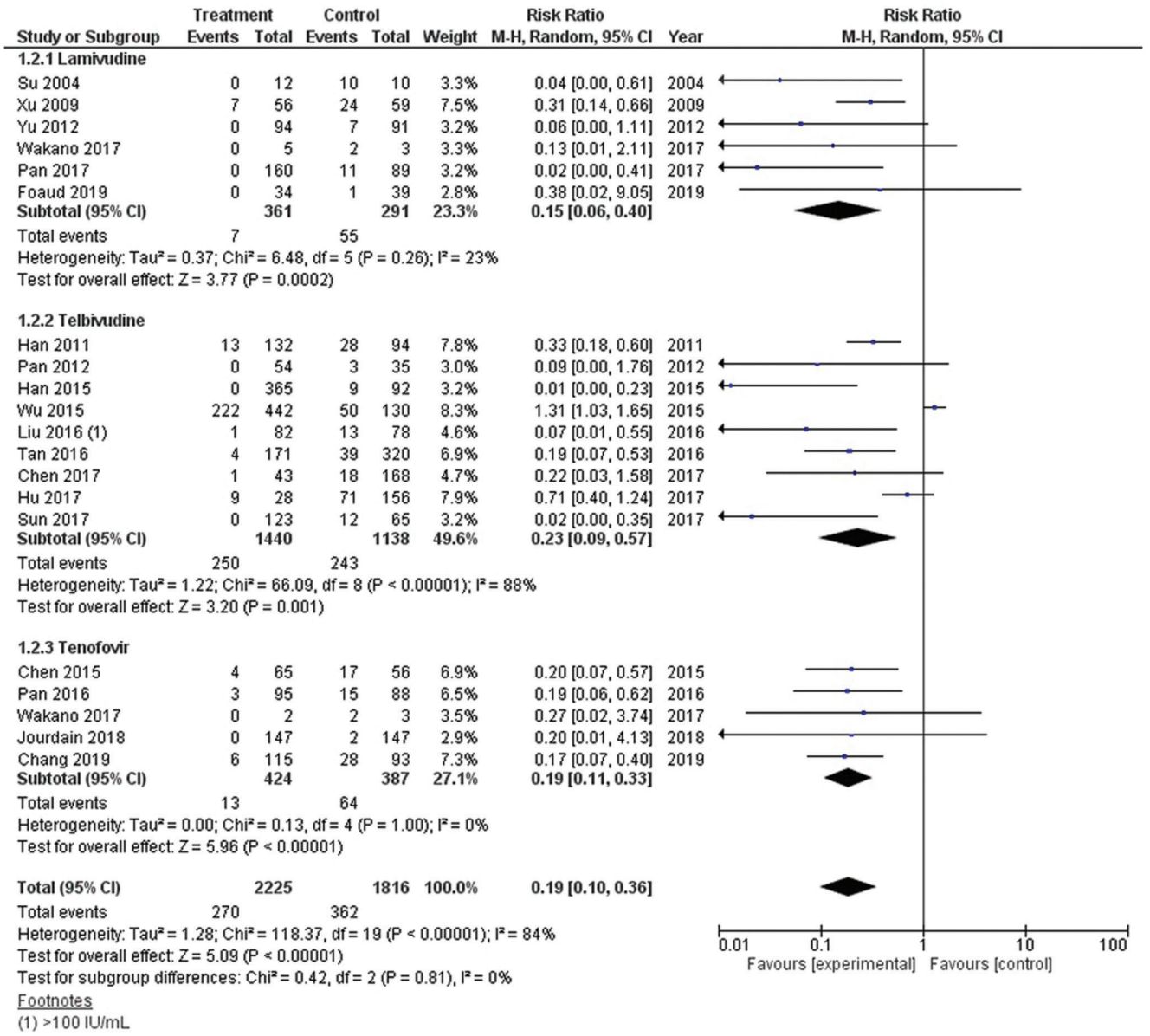

Fig. 3. Forest plots of infant HBV DNA positivity at birth.

Abbreviation: HBV, hepatitis B virus.

in a significant manner. HBeAg loss (LAM: OR [95% CIs] = 1.20 [0.62, 2.33], I^2 = not applicable, *p*-value = 0.59; LdT: OR [95% CIs] = 12.14 [2.17, 67.92], I^2 = 0%, *p*-value = 0.004; TDF: OR [95% CIs] = 3.26 [0.60, 17.73], I^2 = 61%, *p*-value = 0.17) HBeAg seroconversion (LAM: OR [95% CIs] = 1.05 [0.54, 2.02], I^2 = 0%, *p*-value = 0.89; LdT: OR [95% CIs] = 8.93 [2.86, 27.90], I^2 = 7%, *p*-value = 0.0002; TDF: OR [95% CIs] = 1.20 [0.30, 4.85], I^2 = 61%, *p*-value = 0.80).

Interestingly, the LdT groups also led to significant normalizations of alanine aminotransferase levels, as compared with off-therapy controls (OR [95% CIs] = 1.49[1.30, 1.72], I^2 = 0%, *p*-value <0.00001), but not LAM (OR [95% CIs] = 2.47 [0.27, 22.52], I^2 = 97%, *p*-value = 0.42). However, because of the low number of mothers included in the TDF group, as compared to the LdT group, these results might be revised in future analysis.

Publication bias

In order to evaluate publication bias in the studies included, a funnel plot was used. The shape of these plots for each analysis suggests no evidence of publication bias among the studies. As an example, the funnel plot for MTCT is shown in Fig. 6.

Discussion

The rate of new HBV infections has declined by approximately 82% since 1991.[37] However, women of childbearing age with

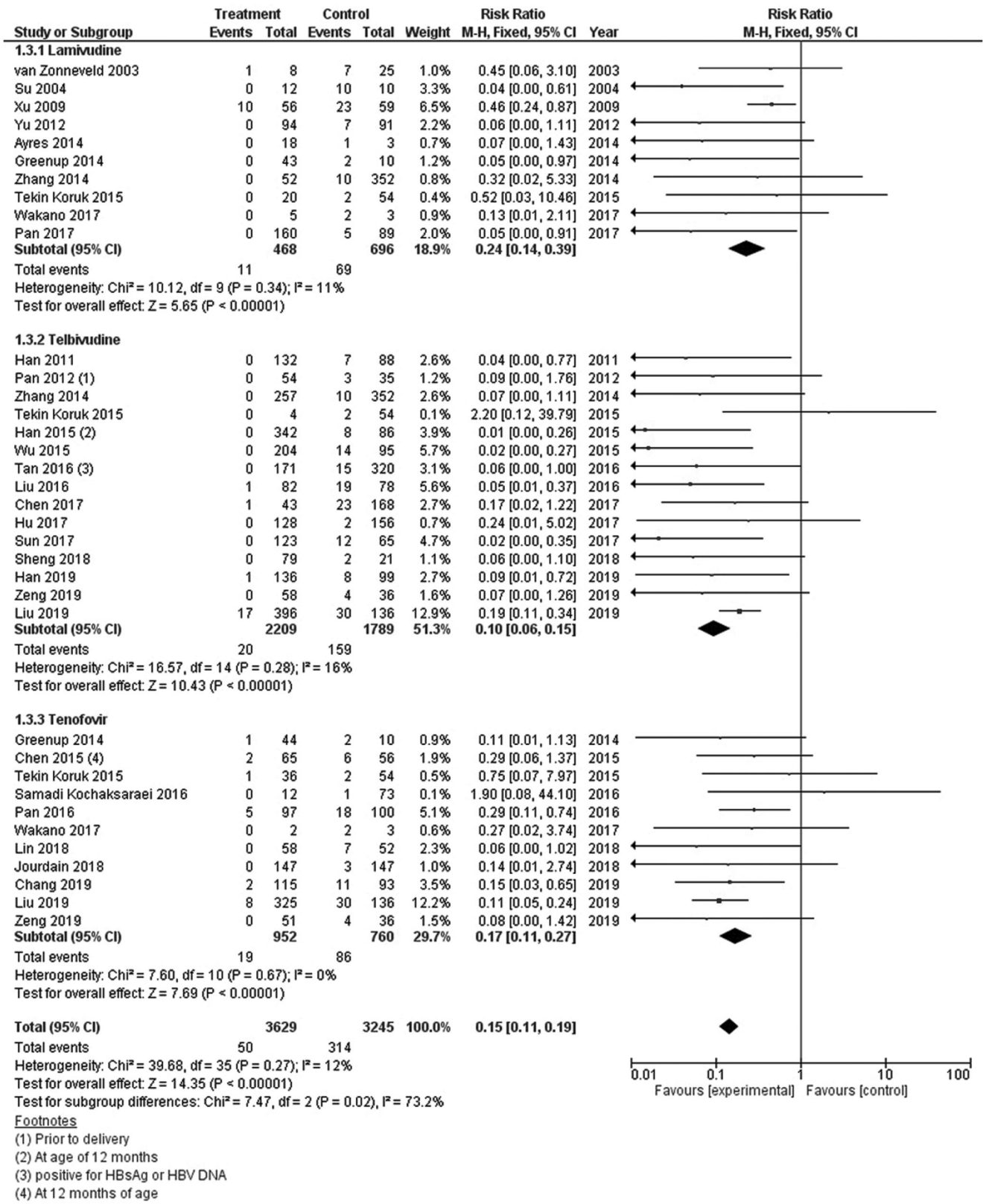

Fig. 4. Forest plots of mother-to-child transmission of HBV infection after 6–12 months.

Abbreviation: HBV, hepatitis B virus.

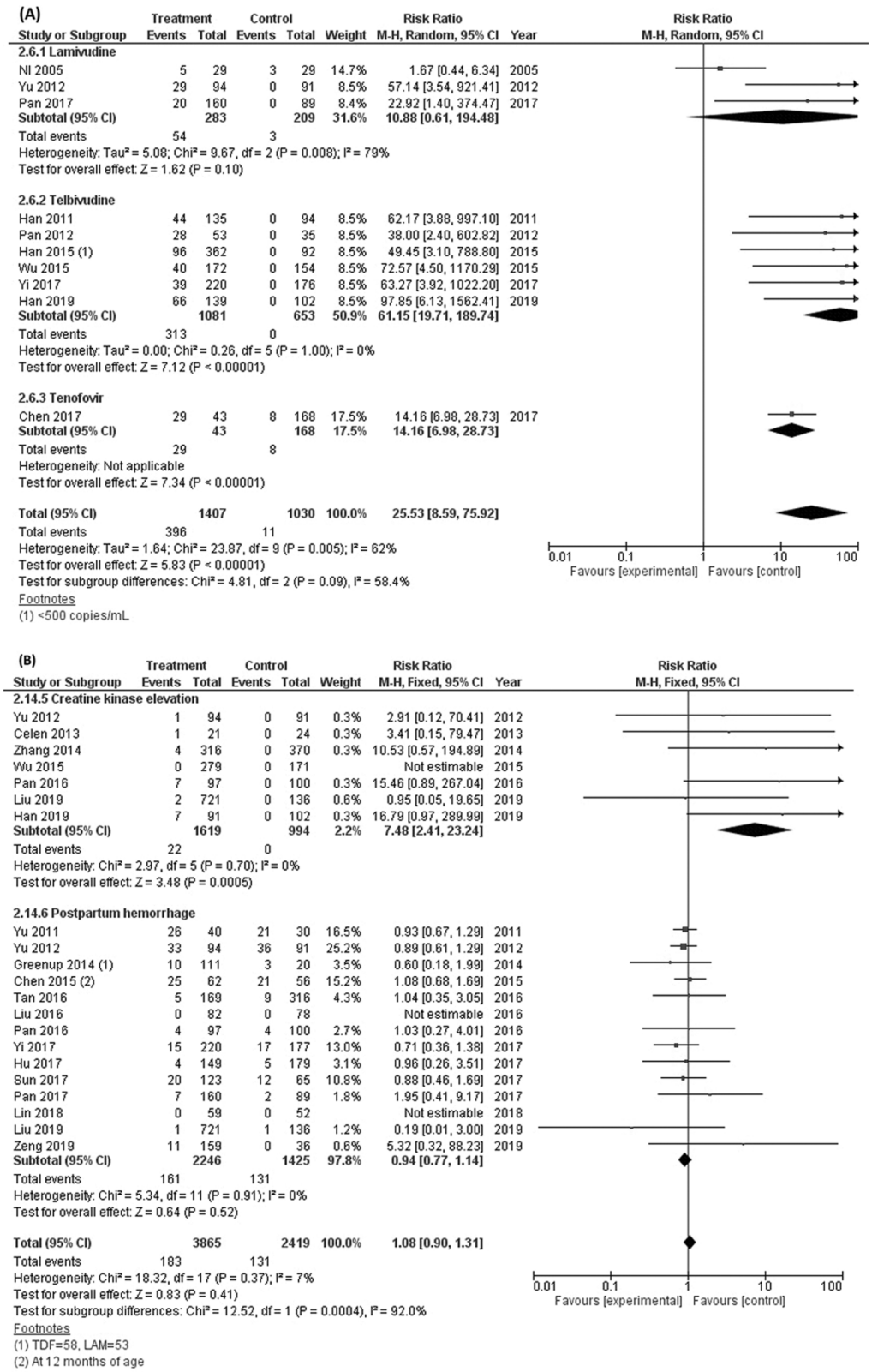

Fig. 5. Forest plots of the rate of making HBV DNA undetectable (A) and creatine kinase elevation, postpartum hemorrhage (B) in mothers following NA therapy during pregnancy.

Abbreviations: HBV, hepatitis B virus; NA, nucleos(t)ide analogue.

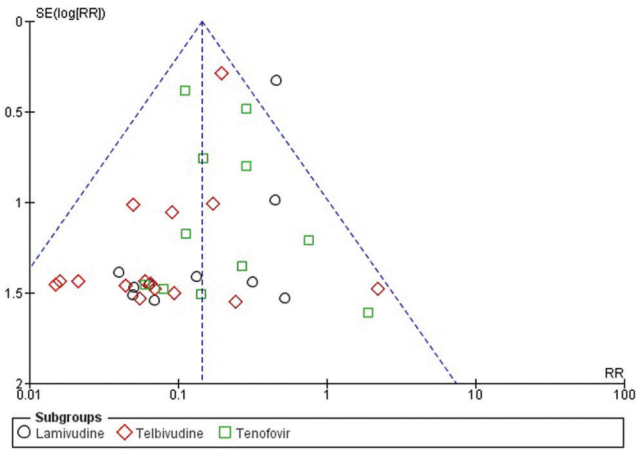

Fig. 6. Funnel plot analysis to examine publication bias for mother-to-child transmission.

CHB infections remain an important source of the continued spread of HBV. Hence, it is critical to prevent the maternal vertical transmission of HBV to reduce the overall number of CHB patients. Pregnant women are vulnerable to several treatments and diseases. In the case of HBV and its associated therapeutic options, several important points should be considered. The capacity of medications to prevent MTCT as well as the safety of both infant and mother are the uppermost considerations. In addition to the comparison of these factors between treatment groups and controls, it is important to identify the drugs with the highest efficacy and the safest profiles for both mother and infant. As mentioned, regardless of drug type, NAs have been shown to be beneficial for pregnant women, while some of their side effects influence both infant and mothers.

The results from the studies analyzed in this study showed that the prevalence of positive HBsAg and/or HBV DNA is significantly lower in a newborn infant from CHB mothers who received antiviral therapy in the second or third trimester. Moreover, they have a greater chance to be non-HBV carriers at 6 months. There are several studies that have reported lower immunoprophylaxis failure as the results of antiviral therapy during pregnancy. Some evidence is also available that implies the roles of antiviral therapy during pregnancy in preventing several other undesirable fetal outcomes, including low birth weight, premature birth, abortion, and death. Mothers may also have greater chances for the suppression of HBV DNA, HBeAg loss/seroconversion, and alanine aminotransferase normalization.

However, there are some risks that could threaten both infants and mothers. One of the most critical ones is the relatively increased but nonsignificant risk of congenital malformations as a result of exposure to NAs. Additionally, mothers exposed to NAs may experience more severe side effects, such as CK elevation. Recently, Brown *et al.*[12] assessed the risk of CK elevation as a result of NA therapy. In contrast to the current study, they could not find any significant association between the CK elevation and NA therapy. Hyun *et al.*[13] also suggested a possible role of TDF therapy in CK elevation in pregnant women but did not find any statistically significant association. The difference in the results might be explained by the attention placed on CK during recent years, or increases in the number of studies analyzed. Selected other outcomes reported in certain published meta-analyses are displayed in Table 2.

According to the European Association for the Study of the Liver recommendations for pregnant women with CHB: (1) those with positive HBsAg should be screened in the first trimester of pregnancy (Evidence level 1, the grade of recommendation 1); (2) in a CHB-infected woman of childbearing age without advanced fibrosis who plans a pregnancy in the future, delaying therapy until the child is born was recommended (Evidence level II-2, the grade of recommendation 1); (3) for pregnant women with CHB and advanced fibrosis or cirrhosis, therapy with TDF is recommended (Evidence level II-2, the grade of recommendation 1); and (4) continuing TDF and switching to TDF in those under treatment with other NAs was also recommended (Evidence level II-2, the grade of recommendation 1; these are consistent with TDF and LdT being in a safer category than LAM (Federal Drug Administration Pregnancy Category B vs. C), and a higher barrier to resistance in TDF than LdT); (5) in pregnant women with either HBV DNA >200,000 IU/mL or HBsAg levels >4 log IU/mL, starting antiviral prophylaxis with TDF at week 24–28 of gestation and continuing for up to 12 weeks after delivery was recommended (Evidence level 1, the grade of recommendation 1). The recommendation to continue for up to 12 weeks might be due to high risk of postpartum alanine aminotransferase level elevation in CHB patients, especially mothers with elevated alanine aminotransferase or HBV DNA levels $\geq$5 $\log_{10}$ IU/mL at delivery.[38]

Compared with other NAs, the number of TDF studies was lower. This may affect the accuracy of analyses associated with this type of drug. During the analysis of factors that contain a low number of studies, NA types were not distinguished. However, those with distinguished results support the high efficacy of LdT. Indeed, in almost all the analyses, LdT was more effective in the reduction of undesirable outcomes associated with both infants and mothers but was not an entirely safe drug.[39] Drug-resistance is one of the most challenging issues related to the treatment of pregnant women with CHB. Interestingly, using LdT in such patients rarely could lead to LdT-related resistance. In the reviewed studies, only Li *et al.*[18] reported an HBV M204I drug resistance mutation at the 40th week of treatment in one patient. However, the others did not report any LdT-resistance development during the study periods.[4,7–9,19,20] This could be explained by the fact that short-term use of LdT is not enough to induce obvious resistance.[9] Analyzing the risk of congenital malformation, no significant difference was found, while neither LAM, LdT, nor TDF, could be presented as an utterly safe drug. Table 2 summarizes the results of previous meta-analyses regarding the efficacy and safety of treatments for CHB during pregnancy.

In spite of the multiple analyses conducted, this study has some limitations, which may affect the selection of drugs for an individual. First, it does not cover treatment and safety predictive factors, such as positivity for HBsAg, baseline levels of HBV DNA, duration of disease, HBV genotypes, and so on. Second, drug resistance – a critical factor for drug choice – was not considered. Third, only journal articles in English language that were indexed in PubMed and Scopus were included in the study. The lack of analysis regarding NAs treatment duration is another limitation of the current study.

In conclusion, it has been shown that NAs therapy is essential for pregnant women with CHB to prevent the

Table 2. Some of the most important reported outcomes in the selected published meta-analysis studies

Study	No of studies	HBsAg positivity	HBV DNA positivity	MTCT	HBV DNA suppression	CK elevation	Postpartum hemorrhage	Congenital malformation	Preterm birth	Fetal/ infant death
Hyun *et al.*[13]	10	0.87 [0.31, 2.40]	0.16 [0.07, 0.39]	0.23 [0.10, 0.52]		8.49 [0.98, 73.28]	0.76 [0.27, 2.16]	1.60 [0.30, 8.47]	2.39 [0.84, 6.81]	1.28 [0.20, 8.25]
Chen *et al.*[49]	5		0.16 [0.07, 0.37]	0.21 [0.07, 0.61]	254.46 [28.39, 2280.79]	9.56 [1.17, 78.09]	0.73 [0.26, 2.07]	1.85 [0.42, 8.18]	2.35 [0.80, 6.94]	1.54 [0.25, 9.56]
Shi *et al.*[50]	10	0.38 [0.15, 0.94]	0.22 [0.12, 0.40]	HBsAg: 0.31 [0.15, 0.63] HBV DNA: 0.20 [0.10, 0.39]						
Lu *et al.*[51]	7			HBsAg:0.09 [0.04, 0.22] HBV DNA: 0.07 [0.02, 0.22]	87.96 [17.03, 454.32]	7.71 [1.99, 29.80]				
Brown *et al.*[12]	26	0.26 [0.16, 0.44]	0.31 [0.20, 0.49]	HBsAg: 0.3 [0.2, 0.4] HBV DNA: 0.3 [0.2, 0.5]	LAM: 57.1 [3.5, 921.4] LdT: RR 5 52.8 [10.7, 261.8] TDF: 45.4 [9.3, 222.5]	Not reported but the difference is not significant	Not reported but the difference is not significant	0.88 [0.21, 3.62]	0.73 [0.35, 1.53]	

Data of the Hyun *et al.*,[13] Chen *et al.*,[49] Shi *et al.*,[50] and Lu *et al.*[51] studies were reported according to OR [95% confidence interval]. Data of the study conducted by Brown *et al.*[12] were reported according to RR [95% confidence interval].

Abbreviations: CK, creatine kinase; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; LAM, lamivudine; LdT, telbivudine; MTCT, mother-to-child transmission; OR, odds ratio; RR, relative risk; TDF, tenofovir.

MTCT of HBV as well as to decrease various undesirable infant outcomes. However, mothers should be warned of the possible risk of elevated CK. Based on the findings, LdT therapy is more effective than others, while more studies on TDF, which has a high barrier to resistance, are needed to clarify TDF efficacy and safety.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Conceptualized the study (ST, SS), performed the literature search and data analysis (AM, MGA, SEB, MA, HSZ, SS), drafted the manuscript (ST), critically revised the work (SS, MD, ST).

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