Efficacy and safety of pregnant women with chronic hepatitis B receiving nucleos(t)ide analogs therapy: a network meta-analysis

Bo Zhu
North China University of Science and Technology https://orcid.org/0000-0001-5221-6901
Xiuli Chen
The fifth affiliated hospital of shijiazhuang
Fumin Feng (fengfumin@ncst.edu.cn)
North China University of Science and Technology
Erhei Dai
https://orcid.org/0000-0001-8835-6199

Research article

Keywords: Lamivudine, Telbivudine, Tenofovir, hepatitis B, mother-to-child transmission

Posted Date: May 13th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-28454/v1

Abstract

Objective

Reducing mother-to-child transmission(MTCT)of hepatitis B virus(HBV) is one of the key ways to eliminate hepatitis B. Although studies have demonstrated the effectiveness of oral nucleos(t)ide analogs(NAs),drug's comparisons are lacking. The network meta-analysis aims to comprehensively compare and summarize the efficacy and safety of the three drugs (Lamivudine(LAM), Telbivudine(TBV) and Tenofovir(TDF)), providing a basis for drug selection.

Methods

A comprehensive retrieval of data was conducted from PubMed (Medline), Web of Science, the Cochrane Library, EMBASE, CNKI and SinoMed through to December 2019. We performed pair-wise meta-analysis and Bayesian network meta-analysis to compare the efficacy and safety of NAs.

Results

A total of 35 studies whith involving a total of 6,109 pregnant women with HBV infenction were selected. All three drugs can effectively block MTCT and improve HBV DNA suppression ($p < 0.05$). No significant differences were found in the occurrence of adverse events in mothers and infants.The results of the network meta analysis showed that the possibility of TBV and TDF being the best drug was 50% and 46%, the possibility of TBV and TDF being the second is the same-45%, the possibility of LAM being the worst drug is 85%.

Conclusion

LAM, TBV and TDF are effective in preventing MTCT of HBV in women with chronic HBV infection with high viral load. Using them does not seem to increase the probability of adverse events in pregnant women and infants. It cannot be ignored that TDF and TBV appear to show better blocking effects in clinical practice.

Background

According to the world health organization report, 257 million people infected with the hepatitis B virus(HBV) develop chronic hepatitis B(CHB), posing a serious threat to human health worldwide. More than 880,000 people die from HBV infection each year due to lack of treatment or inadequate treatment, which is a serious public health problem that deserves global attention (1–3).

Mother-to-child transmission(MTCT) is the main transmission route of HBV. Nearly a third of CHB patients worldwide are caused by mothers who carry positive hepatitis B surface antigen (HBsAg) during delivery. At the same time, the younger you are, the more likely you are to become chronically infected with HBV(4, 5). In order to control hepatitis B in various countries, the hepatitis B vaccine three-needle vaccination is given to newborns. This measure can reduce the HBV infection rate by 75%, and the use of hepatitis B immunoglobulin(HBIG) can reduce it by 90%. (6)Although the hepatitis B vaccine and HBIG combined immunization have achieved good results, 10% -15% of people who are hepatitis B surface antigen (HBsAg) positive still have immune failure(7–9). High level of HBV DNA during pregnancy has been demonstrated to be independent risk factor for MTCT. Studies have shown that as the level of maternal HBV DNA increases (2×10^5IU/mL), the probability of immune failure increases, and the risk of MTCT is nearly 90% (10–15).

Reducing MCTC of HBV is a complex task. It is also one of the key ways to eliminate global hepatitis B. Antiviral therapy is recommended to reduce MTCT of HBV(16).Increasing researchs confirm the effectiveness of the using of nucleos(t)ide analogues(NAs) therapy for women with CHB and high viral loads to reduce MTCT and safety for pregnant women and infants. The choice of drugs has become a controversial issue among liver physicians, obstetricians and pregnant woman infected with HBV. On the other hand, due to public prejudice, less than 1% of mothers with high viral loads have received NAs therapy to avoid MTCT(17). We believe that the previous excellent meta-analysis about antiviral drugs for MTCT of HBV provide a good reference for clinical practices.In fact, due to the late time to market of TDF and the lack of head-to-head studies between two drugs (especially with TDF), it is not good for the choice of drugs in our clinical practices. In this study, we included newly published studies (especially about TDF), as well as more studies on head-to-head comparisons between LAM, TBV and TDF. More notably, for the problem that traditional meta-analysis cannot compare two or more drugs (unless they are compared in the same study), we conducted a network meta-analysis to compare drugs. Through comprehensive analysis of the included studies, indirect data on drug pairwise comparison are obtained. These data can provide the basis for our choice of drugs and provide evidence for pregnancy management of pregnant women with CHB.

Search Strategy

These relevant published studies of the analysis were comprehensively and independently searched by two authors. They searched PubMed(Medline), Web of Science, the Cochrane Library, EMBASE, CNKI and SinoMed up to December 2019, based on the combination of medical subject headings (MeSH) and key words including "lamivudine", "telbivubine", "tenofovir", "hepatitis B", "HBV" and "mother-to-child transmission" (Supplementary Table 1). We also manually retrieved other potentially eligible studies such as reference lists of included studies, systematic reviews and relevant guidelines. Our search is not restricted by language, publisher and publication status.

Inclusion and Exclusion Criteria

Randomized controlled trials(RCTs) and non-randomized controlled trials(NRCTs) are included. In these studies, pregnant women who receive one of the three NAs during pregnancy are both HBsAg and hepatitis e surface antigen (HBeAg) positive and their HBV DNA $\geq 2 \times 10^5$IU/mL.

We excluded patients who were co-infected with HCV, HDV, and HIV, and those who had received α-INF or other antiviral treatment before six months of pregnancy were also excluded. Two independent reviewers use uniform inclusion and exclusion criteria, reconciling by a third independent reviewer if they have disagreements. A total of two rounds of screening were carried out, all the studies being screened based on the title and abstract,then the full text. For studies excluded if they didn't meet the criteria, we record the reasons for exclusion.

Data Extraction and Outcomes

Data extraction was tested using a pre-designed data extraction format, the two researchers used the same standard to extract the data of interest in the included studies after adjustment. Similarly, any differences were reconciled by consensus or by a third researcher. We were mainly interested in the following outcomes: name of the first author, year of publication, type of study, country, patients' baseline characteristics, maternal serum HBV DNA and HBsAg level before delivery, HBV DNA and HBsAg levels in newborns and 6–12 months after birth, and adverse events.

Quality Evaluations of Included Study

The evaluation of research quality was conducted in two parts: RCTs and NRCTs.The Cochrane Risk of Bias assessment tool was used to assess the risk of bias in RCTs. NOS scale was used to assess the quality of observational studies.The former mainly was used to evaluate from the aspects of randomization, allocation concealment, blindness and unknown risk. The latter was used to evaluate the choice and comparability of case and control, exposed and non-exposed or other.

Statistical analysis

Firstly, we performed a traditional meta-analysis on the results to compare the efficacy of antiviral drugs to patients who used the same drug at the same dose. These outcome indicators were expressed as binary variables, then risk ratio (RR) and 95% confidence(95%CI) were calculated. Heterogeneity between studies was evaluated using a chi-squared Q test and I^2 statistics ($p < 0.1$ or $I^2 > 50\%$ considered heterogeneity between studies). When there was no heterogeneity between the combined studies, a fixed-effects model is used, otherwise a random-effects model was used.

Bayesian Markov chain-Monte Carlo model was used for network meta analysis, We incorporate both direct and indirect evidence into our model to compare the efficacy of antiviral drugs if treatments that have not, or cannot be compared directly. P value and 95% CI were evaluated the significance of the outcome. We setted appropriate Model adjustment iterations and Model simulation iterations, they were setted of 20000 and 50000 at the beginning.Model convergence was evaluated by potential scale reduction factor (PSRF). When PSRF was equal to one, it indicates that the model has good convergence and high reliability. The most likely ranking of the effects of each drug was achieved by calculating the Markov chain iteration ratio of each drug, which was represented by a rank probability plot. We also use the node split model to analyze the consistency of direct and indirect comparison results.

During the entire analysis process, if there is heterogeneity, we look for the cause of heterogeneity through subgroup analysis and sensitivity analysis.Statistical indicators I^2 and 95% CI were showed by forest plots. The statistical analysis process was completed using GeMTC 14.3 and Stata 23.0 software.

Results

Search results and study characteristics

Through the developed search strategy, a total of 1,521 articles were retrieved from the listed databases. The search results was listed in Fig. 1. After screening, a total of 35 (18–52)articles were included in the study.Among these studies there were 9 RCTs(18, 19, 23–25, 29, 36, 37, 47) (3(19, 47, 48) multicenter RCTs) and 26 NRCTs(including 23 cohort studies and 3 retrospective studies). Most of these studies occurred in China (27/35), 22 were published in English, and 13 were published in Chinese. There are 30 studies in two arms, of which 9(18–26) studies compared LAM versus control, 12 (28, 30–40)studies compared TBV versus control, 8(42, 44, 46–51) studies compared TDF versus control and 1(29)study compared LAM versus TBV. The remaining five studies were three-arm experiments, including 3(41, 43, 45) studies comparing TBV, TDF versus control, 1(52)study comparing LAM, TDF versus control, and one comparing TBV, LAM versus control. A total of 6,109 pregnant women were included in the 35 studies. Figure 2 is a network of these studies. The characteristics of all the included studies were summarized in Table 1 and the baseline information of the patients, as well as the immunization of the newborns after birth.

Table 1
Characteristics of the included clinical trials in this study

Author,Year	Region	Study design	Intervention	Participants, mothers: infants	Treatment weeks	Age	Baseline HBV DNA Level (Log10 IU/mL)	Baseline ALT(U/L)	Newborn immunization	
									HBIG	HBV vacci
Li,2003	China	RCT	Lamivudine	43:43	LAM 100 mg daily from week 28 of gestation to 4 weeks after delivery	20–40	7.49 ± 0.54		100 IU – 0	10 μg 0.1.6
			control	52:52		20–40	7.05 ± 1.29			
Xu,2009	Singapore	RCT	Lamivudine	89:56	LAM 100 mg daily from week 32 of gestation to week 4 postpartum	26(19–32)	8.6 ± 0.2	0.4(0.1–5.3)×ULN	200 IU – 0	10 μg 0.1.6
			control	61:59		25(20–36)	8.7 ± 0.2	0.4(0.1–0.6)×ULN		
Pan,2016	China	retrospective study	Lamivudine	160:160	LAM 100 mg daily from week 13–26 of gestation to delivery	27.50 ± 3.77	7.24 ± 0.57	49.2 ± 73.6	200 IU – 0	10 μg 0.1.6
			control	89:89	LAM 100 mg daily from week 28–32 of gestation to 12 weeks after delivery	27.08 ± 4.22	7.33 ± 0.47	28.0 ± 35.4		
Zonneveld,2003	netherlands	cohort study	Lamivudine	8:8	LAM 100 mg daily from week 34 of gestation to 6 weeks after delivery		9.3		300 IU – 0	10 μg 2.3.4.
			control	24:25			9.39			
Yu,2012	China	cohort study	Lamivudine	94:94	LAM 100 mg daily from week 24–32 of gestation	26.64 ± 4.17	7.63 ± 0.54	≥ 40	200 IU – 0	10 μg 0.1.6
			control	91:91		25.78 ± 3.89	7.71 ± 0.71	45		
Xiang,2007	China	RCT	Lamivudine	21:21	LAM 100 mg daily from week 28 of gestation to 4 weeks after delivery		8.02 ± 1.15		200 IU – 0	10 μg 0.1.6
			control	18:18			7.16 ± 0.79			

Author,Year	Region	Study design	Intervention	Participants, mothers: infants	Treatment weeks	Age	Baseline HBV DNA Level (Log10 IU/mL)	Baseline ALT(U/L)	Newborn immunization	
									HBIG	HBV vacci
Feng,2007	China	RCT	Lamivudine	48:48	LAM 100 mg daily from week 28 of gestation to 4 weeks after delivery		8.34 ± 1.23		200 IU – 0	10 μg 0.1.6
			control	42:42			8.26 ± 1.87			
Yang,2008	China	RCT	Lamivudine	20:20	LAM 100 mg daily from week 28 of gestation to 4 weeks after delivery	20–40	(3.6 ± 2.5)copy/ml		200 IU – 0	10 μg 0.1.6
			control	20:21		20–40	(2.9 ± 2.0)copy/ml.			
Jiang,2012	China	cohort study	Lamivudine	164:164	LAM 100 mg daily from week 24–30 of gestation	27.30 ± 4.44	7.83 ± 0.76	39.58 ± 44.26	200 IU – 0	20 μg 0.1.6
			control	92:92		26.44 ± 3.17	7.93□0.58	42.23 ± 40.40		

Author,Year	Region	Study design	Intervention	Participants, mothers: infants	Treatment weeks	Age	Baseline HBV DNA Level (Log10 IU/mL)	Baseline ALT(U/L)	Newborn immunization	
									HBIG	HBV vacci
Zhang,2014	China	prospective - open - NRCT	Lamivudine	55: 54	LAM 100 mg daily from week 28–30 of gestation to 4 weeks after delivery	28.42 ± 7.12	7.62 ± 0.37	39.65 ± 26.37	200 IU – 0	20 μg 0.1.6
			Telbivudine	263:262	TBV 600 mg daily from week 28 of gestation to 4 weeks after delivery	29.78 ± 6.31	7.69 ± 0.44	30.06 ± 27.86	200 IU – 0	20 μg 0.1.6
			control	374:370		28.97 ± 4.59	7.58 ± 0.45	29.53 ± 20.72	200 IU – 0	20 μg 0.1.6
Han,2011	China	prospective - open - NRCT	Telbivudine	135:132	TBV 600 mg daily from week 20–30 of gestation to 4 weeks after delivery	27(20–38)	8.10 ± 0.56	35.67 ± 43.41	200 IU – 0	10 μg 0.1.6
			control	94:94		26(20–35)	7.98 ± 0.61	42.53 ± 40.13	200 IU – 0	10 μg 0.1.6

Author,Year	Region	Study design	Intervention	Participants, mothers: infants	Treatment weeks	Age	Baseline HBV DNA Level (Log10 IU/mL)	Baseline ALT(U/L)	Newborn immunization	
									HBIG	HBV vacci
Yu,2014	China	RCT	Telbivudine	233:245	TBV 600 mg daily from week 20–32 of gestation to delivery	26.81 ± 3.85	7.77 ± 0.81	48.84 ± 75.30	200 IU – 0	20 μg 0.1.6
			Lamivudine	154:159	LAM 100 mg daily from week 28 of gestation to delivery	26.66 ± 3.48	7.66 ± 0.71	57.60 ± 83.54	200 IU – 0	20 μg 0.1.6
Sheng,2018	China	prospective - open - NRCT	Telbivudine	91:91	TBV 600 mg daily from week 32 of gestation	27.8 ± 4.17	8.15 ± 0.82	26.53 ± 8.32	100 IU – 0	10 μg 0.1.6
			control	21:21		26.8 ± 3.66	8.09 ± 1.04	23.62 ± 6.51	100 IU – 0	10 μg 0.1.6
Liu,2016	China	cohort study	Telbivudine	A: 50:50	TBV 600 mg daily from first trimester or second trimester to 4 weeks after delivery	27.88 ± 3.73	7.67 ± 0.79	46.64 ± 58.74	100 IU – 0	10 μg 0.1.6
				B:32:32	TBV 600 mg daily from third trimester to 4 weeks after delivery	28.31 ± 3.81	7.46 ± 0.73	28.91 ± 38.48	100 IU – 0	10 μg 0.1.6
			control	78:78		27.46 ± 3.47	7.56 ± 0.57	30.87 ± 28.99	100 IU – 0	10 μg 0.1.6
Han,2015	China	prospective - open - NRCT	Telbivudine	A:257:259	TBV 600 mg daily from second trimester	27(20–35)	7.91(6–9.0)	21.45(7.6–407.0)	200 IU – 0	20 μg 0.1.6
				B:105:106	TBV 600 mg daily from third trimester	28(20–38)	7.83(6–9.1)	17.1(5.2–513.5)	200 IU – 0	20 μg 0.1.6
			control	92:92		26(20–35)	7.93(6–9.5)	26.55(8.1–262.5)	200 IU – 0	20 μg 0.1.6
Yi,2017	China	cohort study	Telbivudine	A:41:41	TBV 600 mg daily from week 28 of gestation	31.54 ± 4.21	1.50 ± 0.62	15.19 ± 8.53	200 IU – 0	10 μg 0.1.6
				B:179:179	TBV 600 mg daily from week 28 of gestation	27.77 ± 3.48	8.05 ± 0.37	21.58 ± 13.15	200 IU – 0	10 μg 0.1.6
			control	176:176		28.27 ± 3.65	7.94 ± 0.62	18.85 ± 9.83	200 IU – 0	10 μg 0.1.6

Author,Year	Region	Study design	Intervention	Participants, mothers: infants	Treatment weeks	Age	Baseline HBV DNA Level (Log10 IU/mL)	Baseline ALT(U/L)	Newborn immunization	
									HBIG	HBV vacci
Pan,2012	China	cohort study	Telbivudine	53:54	TBV 600 mg daily from week 12–30 of gestation	27(21–34)	8.08(6.62–9.45)	60.40(41.40–422.00)	200 IU – 0	20 μg 0.1.6
			control	35:35		27(21–33)	8.08(6.76–9.08)	63.20(42.40–262.50)	200 IU – 0	20 μg 0.1.6

We evaluated the quality of all the studies. Since most of the studies are NRCTs, they are difficult to control the allocation and blindness, and there is a high risk of bias. However, because the researchers better maked the patients in each group take medicine in compliance, so the risk of bias is low. Our assessment of the risk of bias was showed in Fig.S1. All analyses were based on previous published studies, no ethical approval and patient consent are required.

Effectiveness of Nas Therapy: Newborns

HBsAg positive rate during delivery

Of the 11 studies that included lamivudine and the control group, HBsAg positive rates in newborns is reported in 8(18–20, 22–24, 26, 27) studies.The newborn HBsAg positive rates were 18.13%(116/640)in the LAM group and 27.06%(220/813) in the control group, repectively. Merging using a random-effects model, the results show that newborn HBsAg seropositivity was statistically lower in the LAM groups□RR = 0.58,95%CI = 0.39–0.87,P = 0.007, I^2 = 61.9%□. To reduce heterogeneity, we perform subgroup analysis based on the type of study (RCTs and NRCTs). The result showed the LAM group was no statistically significant difference in all RCTs□RR = 0.47,95%CI = 0.17–1.26,P = 0.132□I^2 = 69.4%□, but lower than the control group in NRCTs□RR = 0. 60,95%CI = 0.39–0.92□P = 0.020□I^2 = 64.5%□. But it should be noted that there was a trend towards a decrease in all RCTs□16.07% vs. 25.73%□.

Of the 16 studies that included TBV and the control group, 13(27, 28, 30–32, 34, 36, 38–41, 43, 45) studies reported HBsAg positive rates in newborns.The newborn HBsAg positive rates were 10.36%(133/1284)in the TBV group and 24.92%□236/947) in the control group, respectively. Because these studies are all NRCTs, the random-effects model was applied to calculate the overall effects. The HBsAg positive rate in the TBV group was sigenificantly lower than the control group[RR = 0.33,95%CI = 0.22–0.50,P < 0.05].

7(41, 43, 45, 47–49, 51)(7/12) studies reported HBsAg positive rate in newborns. We merged these studies and used a random-effects model to calculate the overall effects. The newborn HBsAg positive rates were 5.91%(28/474)in the TDF group, versusing 15.81%□68/430). Oraling TDF during pregnancy can effectively reduce the HBsAg positive rate in infants at birth .[RR = 0.42,95%CI = 0.21–0.82,p = 0.011□I^2 = 43.6%].All the results were showed in Fig. 3.

Hbv Dna Positive Rate During Delivery

Among the 35 studies, 18(5 of LAM(19, 20, 22, 24, 26), 8 of TBV (28, 31, 32, 34, 35, 38, 43, 45), 5 of TDF(43, 45, 47, 48, 51))studies reported the HBV DNA positive rate of newborns. We use the random-effects model to calculate their overall effects separately. The positive rates of HBV DNA in the newborns of the two NAs therapy groups (LAM and TBV)were statistically lower.[LAM:RR = 0.21,95%CI = 0.09–0.49,p = 0.000,I^2 = 47.4%.TBV:RR = 0.10,95%CI = 0.04–0.22,p = 0.000, I^2 = 43.3%]. We excluded the study Chen et al(51) which caused high heterogeneity through sensitivity analysis [95%CI = 0.091–0.326]. Analysis showed the same result. [RR = 0.17, 95%CI = 0.09–0.33, p = 0.000,I^2 = 0.00%] .

Hbsag Positive Rate Of 6–12 Month Infants

There were 8(19–21, 24–27, 52) studies of LAM, 15(27, 28, 30–38, 40, 41, 43, 45) studies of TBV nd 12(41–52) studies of TDF reporting HBsAg positive rates in infants aged 6–12 months. Compared with the control group, NAs therapy can reduce the HBsAg positive rate of infants at 6–12 months of age.The difference is statistically significant [LAM: RR = 0.36, 95%CI = 0.21–0.61,p = 0.000,I^2 = 10.3%.TBV:RR = 0.12,95%CI = 0.06–0.24,p = 0.00,I^2 = 35.6%.TDF:RR = 0.14,95%CI = 0.07–0.28,p = 0.000,I^2 = 0.00%,Fig. 4]. The three drugs could reduce the HBsAg positive rates by 6.98%, 9.99%, and 7.74%, respectively.

Hbv Dna Positive Rate Of 6–12 Month Infants

A network meta-analysis was performed on the HBV DNA positive rate of infants aged 6–12 months reported in studies. The results were consistent with the results of the direct meta-analysis. Treatment with NAs is effective, but there is no reliable comparison between drugs.(Table.3)

Net-work Meta Results

HBsAg positive rate of 6–12 month infants

The Bayesian Markov Chain-Monte Carlo model parameter values were set to: number of chains was 4, tuning iterations was 2000, simulation iterations was 5000, initial values scaling was 2.5, and thinning interval was 10, at this time the model has good convergence with PSRF being 1, and when the number of occurrences is zero, we also add a value to the number of non-occurrences at the same time to correct the model accuracy .

Random-effects standard deviation of the inconsistency model and the consistency-model did not show a significant deviation and the inconsistency test performed by the node split method showed that there were no local inconsistencies ($P > 0.05$). In summary, a net meta-analysis was performed on the HBsAg-positive rate of infants aged 6–12 months reported in 31 studies by using a consistent effect model. The results of the summary analysis were showed in Table 2. The use of any antiviral drug can significantly reduce the HBsAg positive rate than without the drug, but we have no sufficient reason to believe that the results of pair-wise comparison of the three drugs are reliable(95% confidence interval does not include 1).

Table 2
The results of network meta analysis of HBsAg positive rates in infants at 6–12 months

Author,Year	Region	Study design	Intervention	Participants, mothers: infants	Treatment weeks	Age	Baseline HBV DNA Level (Log10 IU/mL)	Baseline ALT(U/L
Wu,2015	China	prospective -NRCT	Telbivudine	279:280	TBV 600 mg daily from week 24–32 of gestation to 4 weeks after delivery	27(17–38)	7.26 ± 0.50	111(45-
			control	171:130		28(18–40)	7.40 ± 0.65	134(44-
Zhang,2009	China	RCT	Telbivudine	31:31	TBV 600 mg daily from week 28–32 of gestation	20–40	7.38 ± 0.81	
			control	30:30		20–40	7.46 ± 0.45	
Zhao,2010	China	RCT	Telbivudine	30:30	TBV 600 mg daily from week 28 of gestation to 4 weeks after delivery			
			control	30:30				
Zhang,2010	China	prospective - open - NRCT	Telbivudine	30:30	TBV 600 mg daily from week 28of gestation			
			control	30:30				
Zeng,2010	China	cohort study	Telbivudine	22:22	TBV 600 mg daily from week 28 of gestation		7.66□0.82	
			control	26:26			7.13 ± 1.29	
Yao,2011	China	prospective - open - NRCT	Telbivudine	28:28	TBV 600 mg daily from week 28 of gestation		7.5 ± 0.6	93.6 ± 2
			control	30:30			7.5 ± 0.7	50.5 ± 5
Zeng,2019	China	retrospective study	Telbivudine	58:58	TBV 600 mg daily from week 20–28 of gestation to 12 weeks after delivery	27.2 ± 10.8	7.88 ± 0.65	127.3 ±

Author,Year	Region	Study design	Intervention	Participants, mothers: infants	Treatment weeks	Age	Baseline HBV DNA Level (Log10 IU/mL)	Baseline ALT(U/L
			Tenofovir	51:51	TBV 600 mg daily from week 20–28 of gestation to 12 weeks after delivery	26.5 ± 9.5	7.91 ± 0.75	143.3 ±
			control	36:36		25.7 ± 10.9	7.69 ± 0.53	132.3 ±
Shen,2019	China	cohort study	Tenofovir	40:40	TDF 300 mg daily from third trimester to delivery	25.4 ± 3.4	7.34 ± 0.65	21.7 ± 5
			control	31:31		25.1 ± 3.0	7.21 ± 0.76	20.5 ± 4
Xiao,2017	China	prospective -NRCT	Tenofovir	60:62	TDF 300 mg daily from week 28 of gestation to 4 weeks after delivery	27. 62 ± 3. 19	7. 62 ± 0. 39	20. 13 ±
			Telbivudine	60:63	TBV 600 mg daily from week 28 of gestation to 4 weeks after delivery	28. 56 ± 3. 22	7. 56 ± 0. 41	19. 26 ±
			control	60:60		28. 45 ± 3. 59	7. 52 ± 0. 56	22. 05 ±

Author,Year	Region	Study design	Intervention	Participants, mothers: infants	Treatment weeks	Age	Baseline HBV DNA Level (Log10 IU/mL)	Baseline ALT(U/L)
Xiao,2017	China	prospective -NRCT	Tenofovir	60:62	TDF 300 mg daily from week 28 of gestation to 4 weeks after delivery	27. 62 ± 3. 19	7. 62 ± 0. 39	20. 13 ± 13. 29
			Telbivudine	60:63	TBV 600 mg daily from week 28 of gestation to 4 weeks after delivery	28. 56 ± 3. 22	7. 56 ± 0. 41	19. 26 ± 11. 52
			control	60:60		28. 45 ± 3. 59	7. 52 ± 0. 56	22. 05 ± 12. 52
Wang,2019	China	prospective -NRCT	Tenofovir	128:128	TDF 300 mg daily from week 28 of gestation	29.48 ± 3.83	7.87 ± 0.51	16.5
			control	72:72		28.73 ± 4.15	7.83 ± 0.65	14
Chen,2017	China	prospective -NRCT	Tenofovir	30:30	TDF 300 mg daily from week 28 of gestation to delivery	30.3 ± 5.9	7.50 ± 0.50	70.40 ± 15.44

Author,Year	Region	Study design	Intervention	Participants, mothers: infants	Treatment weeks	Age	Baseline HBV DNA Level (Log10 IU/mL)	Baseline ALT(U/L
			Telbivudine	79:79	TBV 600 mg daily from week 28 of gestation to delivery	30.3 ± 5.9	7.32 ± 0.80	72.55 ± 18.43
			control	44:44		30.3 ± 5.9	7.50 ± 0.55	68.98 ± 16.35
Samadi Kochaksaraei, 2016	Canada	cohort study	Tenofovir	23:24	TDF 300 mg daily from week 28–32 of gestation to 12 weeks after delivery	30(28–34)	7.7(3.2–8.1)	30(18–50)
			control	138:146		32(29–36)	2.3(1.6–3.1)	17(12–24)
Chang,2019	Taiwan, China	cohort study	Tenofovir	110:115	TDF 300 mg daily from week 30–32 of gestation to 4 weeks after delivery	32.84 ± 3.57	8.25 ± 0.48	20.88 ± 28.94
			control	91:93		32.69 ± 3.36	8.29 ± 0.49	19.10 ± 23.85
Lin,2018	China	cohort study	Tenofovir	59:58	TDF 300 mg daily from week 24–28 of gestation	28.31 ± 3.56	7.44 ± 0.80	54.62 ± 105.7
			control	52:52		28.06 ± 3.42	7.66 ± 0.55	57.5 ± 103.3
Celen,2013	Turkey	retrospective study	Tenofovir	21:21	TDF 300 mg daily from week 18–27 of gestation to 4 weeks after delivery	28.2 ± 4.1	8.28	56(22–71)
			control	24:23		26.9 ± 2.9	8.31	52(19–77)
Greenup,2014	Australia	cohort study	Tenofovir	58:43	TDF 300 mg daily from week 32 of gestation to 12 weeks after delivery	30 ± 8.5	7.94 ± 0.78	28(22–36)
			Lamivudine	52:44	LAM 100 mg daily from week 32 of gestation to 12 weeks after delivery	28 ± 5.3	7.72 ± 0.61	22(18–30)
			control	20:10		28 ± 5	8 ± 0.04	25(17–31)
Chen,2015	Taiwan, China	prospective - open - NRCT	Tenofovir	62:65	TDF 300 mg daily from week 30–32 of gestation to 4 weeks after delivery	32.41 ± 3.12	8.25 ± 0.45	23.27 ± 36.2
			control	56:56		32.45 ± 3.2	8.24 ± 0.35	16.59 ± 14.43
Author,Year	Region	Study design	Intervention	Participants, mothers: infants	Treatment weeks	Age	Baseline HBV DNA Level (Log10 IU/mL)	Baseline ALT(U/L)
Pan,2016	China	RCT	Tenofovir	97:95	TDF 300 mg daily from week 30–32 of gestation to 4 weeks after	27.4 ± 3.0	8.2 ± 0.5	23.0 ± 22.4

Author,Year	Region	Study design	Intervention	Participants,	delivery	Treatment weeks	Age	Baseline HBV DNA Level	Baseline ALT(U/L
			control	100;88 mothers: infants			26.8 ± 3.0	8.0 ± 0.7 (Log10 IU/mL)	20.5 ± 15.4

Table 3
The results of network meta analysis of HBV DNApositive rates in infants at 6–12 months

Con			
5.91 (1.64, 29.90)	LAM		
19.37 (7.63, 72.49)	3.24 (0.64, 17.33)	TBV	
18.68 (5.39, 88.73)	3.08 (0.49, 21.43)	0.95 (0.19, 4.79)	TDF
Con			
14.26 (1.06, 592.97)	LAM		
85.34 (7.69, 2336.61)	5.76 (0.09, 346.08)	TBV	
27.62 (1.14, 2802.01)	1.98 (0.02, 281.54)	0.34 (0.01, 33.61)	TDF

We sortted the effects of three antiviral drugs on blocking MTCT by drawing the figure of rank probability. LAM was most likely to be the drug with the worst effect that blocks MTCT of HBV. TBV and TDF have the same probability of medium effect.The possibility of TBV and TDF being the most effective drugs were 45% and 50%(Fig. 5)

Safety Of Nas Therapy: Infants

Apgar scores, length, weight at birth, congenital malformations and preterm birth data were used to assess the safety of the NAs therapy for the infant. Interestingly, despite studies reporting low birth weight infants, we did not find that the babies who is in the NAs group had significantly different weights at birth[WMD=-0.03,95%CI=-0.06-0.00,p = 0.151, I^2 = 24.0%. Figure 6]. In addition, the Apgar score and height of the infants in the treatment group did not increase or decrease. [Apgar:WMD=-0.00,95%CI=-0.02-0.02,p = 0.991,I^2 = 0.0%.Fig.S2;Height:WMD = 0.03,p = 0.170,95%CI=-0.07-0.12,I^2 = 22.3%.Fig.S3]. Three studies reported the NAs therapy does not cause premature babies. Congenital malformations were reported in five studies, and it is worth noting that researchers evaluated that the occurrence of these adverse events was independent of medication.

Effectiveness And Safety Of Nas Therapy: Mother

26 studies reported baseline HBV DNA levels and HBV DNA levels during delivery of mothers. The random-effects model was used to calculate the combined effects and the results showed that HBV DNA levels at delivery were significantly lower than at baseline(SMD = 4.68,95%CI = 4.27–5.09). We evaluated the effects of the drug on cesarean section, postpartum hemorrhage, and the occurrence of elevated creatine kinase in pregnant women. No antiviral medication has increased cesarean delivery[LAM:RR = 0.95, 95%CI = 0.84–1.07, p = 0.391, I^2 = 35.6%.TBV:RR = 1.06, 95%CI = 0.96–1.18, p = 0.262, I^2 = 0.00%. TDF:RR = 1.09, 95%CI = 0.95–1.25, p = 0.239, I^2 = 0.00%.] and postpartum hemorrrhage in pregnant women[LAM:RR = 1.0, 95%CI = 0.79–1.26, p = 0.391,I^2 = 0.00%. TBV:RR = 0.97, 95%CI = 0.60–1.58,p = 0.262□I^2 = 0.00%.TDF: RR = 1.18,95%CI = 0.97–1.44,p = 0.239,I^2 = 0.00%.]. Pregnant women are not more likely to cause elevated creatine kinase[LAM:RR = 4.68,95%CI = 0.82–26.74,p = 0.084,I2 = 0.00%.TBV:RR = 2.13,95%CI = 0.79–5.74,p = 0.137, I^2 = 36.8%.TDF: RR = 7.83, 95%CI = 0.95–64.74,p = 0.056,I^2 = 0.00%.].Pregnant women's HBeAg seroconversion and ALT normalization were also evaluated. There was no statistical difference in HBeAg seroconversion [LAM:RR = 3.26,95%CI = 0.58–18.39,p = 0.181, I^2 = 0.00%. TBV:RR = 1.25,95%CI

= 0.22–7.08, p = 0.800, I^2 = 0.00%.TDF: RR = 1.69,95%CI = 0.17–17.11, p = 0.659,I^2 = 55.8%.] Three studies reported ALT normalization rates in the LAM group.It showed no significant difference. [RR = 1.84,95%CI = 0.80–4.24,p = 0.152□I^2 = 87.0%]

A multicenter prospective cohort study by Xu(19) et al. states that for mothers with elevated ALT at baseline, the median ALT levels decreased to 1xULN at 4 and 6 weeks after administration in both groups, respectively. But, it increased again at 4 weeks after delivery in no NAs therapy. ALT normalization rate in TBV group was higher than that in control group[RR = 1.55,95%CI = 1.24–1.95, p = 0.00,I^2 = 0.00%]. Only one study(50) reported rates of ALT normalization in the use of TDF. The study noted that mothers receiving TDF had higher rates of ALT normalization (82% vs 61%). Pan et al.(47) pointed out that those patients with ALT levels that were 10 times above the normal range had alanine aminotransferase flares resolved after the initiation of antiviral therapy. Research by Chen et al.(51) found that during the study period, the incidence of ALT elevation > 2 xULN in the TDF group over 3 months was significantly lower than that in the control group (3.23% vs 14.29%, P = 0.0455).

Publication Bias

We used funnel plots to evaluate publication bias in included studies. Due to limited data resources available for the study, we only performed publication bias detection for the main outcome, MTCT rate.The results of funnel plot showed good symmetry and dispersion among the studies. There was no significant

publication bias(Fig. 7).

Discussion

MTCT mainly refer to intrauterine transmission, transmission during delivery and transmission through nursing or breast milk(53). In areas with high hepatitis B prevalence, at least half of them develope from HBV infection during perinatal or early childhood(54). Hepatitis B vaccine is believed to be effective in preventing HBV infection, especially for babies born to mothers who carry hepatitis B virus. In addition, HBIG is recommended for babies born to HBeAg-positive mothers on the basis of vaccination(55). Use of HBV vaccine and HBIG within 12 hours of birth, followed by two additional HBV vaccination inoculations, has been demonstrated to reduce the MTCT rate from 90% to approximately 5%-10%(56, 57). However, these 5% -10% of people who have failed immunity will enter a chronic hepatitis state once their condition is not effectively controlled. As the condition worsens, decompensated cirrhosis and liver failure may occur, and they may develop liver cancer, eventually dying(58). High HBV DNA load in pregnant women is a key risk factor for immune failure(11, 59, 60). It is estimated that the risk of HBV vertical transmission is more than 90% when the maternal viral load is greater than 2×10^5 IU /ml. Amniocentesis performed on HBV infected mothers with HBV DNA level higher than 2×10^7IU/ml significantly increased the frequency of vertical HBV transmission (60–62). Guidances from the European Association for the Study of Liver, the American Association for the Study of Liver Diseases, and the Asian Pacific Association for the Study of the Liver recommend that antiviral treatment should be used for pregnant women with hepatitis B virus to avoid MTCT(63–65).

LAM was the first approved nucleoside reverse transcriptase inhibitor that has therapeutic effect on HBV and the first drug used to block MTCT of HBV. Long-term clinical practice has proved its good effect.However, in the course of treatment, it was prone to drug resistance mutations(66, 67).TBV is a class of deoxynucleoside drugs approved by FDA in 2006 and China in 2007.Drug resistance and virological breakthrough were lower than lamivudine in numerous clinical trials(68, 69). TDF is a nucleotide analogue that inhibits reverse transcriptase and ribonucleic acid, and has been shown to be effective and safe in HIV or HBV single infection and co-infection in a number of studies with virtually no drug resistance(70–72).

The U.S. food and drug administration classified TBV and TDF as category B pregnancy (animal experiments found no has any harm to the embryos, but it is lack of clinical studies in pregnant women), LAM, ADV and ETV as pregnancy category C drugs (animal experiments prove that the fetus has teratogenic effect, but did not study in pregnant women).In this analysis, we included a total of 35 studies involving 6,109 pregnant women with HBV DNA $\geq 2 \times$ 105 IU/mL. The results of direct meta-analysis showed that the HBsAg serum positive rate of the three antiviral treatment groups was significantly lower than that of the control group at birth. More importantly, the combined results of 6–12 months showed that antiviral treatment could effectively reduce the incidence of MTCT,. In addition, antiviral drugs have also shown a good effect in reducing HBV DNA load in pregnant women, and NAs therapy can better inhibit HBV DNA level in babies born. We performed a reticulated meta-analysis to compare three antiviral drugs. The results also showed the effectiveness of antiviral drugs for treatment. However, because there are fewer RCTs experiments available, there are fewer studies comparing pairs, Comparisons between drugs are not reliable.According to the comparison of grade probabilities, we found that TBV and TDF showed greater advantage than LAM in blocking MTCT of HBV, but the relative advantage of TDF and TBV was difficult to determine, and the probability of TBV being the best drug was 4% higher than TDF. TDF, which was first reported in 2012 for the prevention of MTCT has had few high-quality clinical studies, which may account for its lack of superiority in this meta-analysis(73). In recent years, some scholars have done clinical studies or other meta-analyses comparing the two, and the conclusions have been somewhat controversial. In the study by Zeng et al., There were no cases of MTCT in 51 and 58 infants delivered in the TDF group and TBV group, respectively. Among the 32 infants in the untreated group, 4 had hepatitis B Antigen positive, the difference was statistically significant ($p < 0.01$). The study by Xiao et al. also obtained the same result (0/60 vs 0/62, $p < 0.05$). However, in the study of Chen et al., the serological positive rate of HBsAg in 12-month-old infants showed a difference between the TBV group and the TDF group (3.79% vs. 3.33%,$p < 0.05$), indicating that tenofovir was slightly more effective.However, these comparison samples are small and not RCT, so the conclusions may be biased. Deng(74). conducted a meta-analysis of 306 mothers receiving tibivudine and 270 mothers not receiving antiviral drugs. Serological positive rates of HBsAg and HBV DNA in infants in the tibivudine group were significantly lower at birth and 6–12 months later.

In the systematic evaluation conducted by Brown et al.(75) the efficacy and safety of LAM, TBV and TDF for pregnancy were evaluated. The results showed that antiviral drugs not only significantly reduced the incidence of MTCT, but also that the former two drugs were safe for pregnant women and did not increase the incidence of adverse events in infants. However, the safety of TDF was not described in this study, perhaps because of the limited number of studies involving the safety of tenofovir that could be included and the lack of controlled outcome data.

In our analysis, although there is less study on drug safety data, according to the existing evidence to merge, no matter what kind of medication was not increased pregnant women cesarean section rate and the rate of postpartum hemorrhage, and did not cause higher CK. These limited safety data prove that our antiviral treatment is feasible. However, these studies show that pregnant women are receiving treatment for a short period of tim and also lack of data on maternal and fetal late effects. This requires researchers to obtain through long-term follow-up.

The strength of this analysis is that we comprehensively and thoroughly evaluate the information contained in the included studies, which includes both newly published studies and later TDF what is used for clinical lately. We have not only conducted traditional meta-analysis, but also used Bayesian network model analysis to solve the shortcomings of the lack of comparative study between drugs in reality, obtaining comparisons between drugs indirectly. However, there are still many shortcomings. First, due to the limited published RCTs, more NRCTs was included, which also expanded the low quality of evidence. However, these NRCTs are not the cause of greater heterogeneity in subgroup analysis. Second, more of the included studies were from Chinese studies, which made the results limited to the global scale. Third, there are fewer head-to-head studies between the two drugs included, which results in low reliability of the combined results, which is also reflected in our network analysis. Fourth, we did not integrate more factors, such as drug resistance, hepatitis B virus genotype, cost-effectiveness and so on.

We also need more multicenter, rct studies comparing head-to-head comparisons between drugs, especially more studies comparing the effectiveness and safety of TBV and TDF. This allows us to have more high-quality evidence in the choice between the two drugs, so that we can obtain both direct evidence and more reliable indirect evidence through meta-analysis.

In conclusion, we found that it is effective and safe to block MTCT of HBV through Nas therapy for pregnant women with CHB and high viral load in the body through analysis. TBV and TDF are more effective than LAM. TBV and TDF have similar blocking effects.However, because of the higher resistance of TBV than TDF, we seem to recommend the use of TDF.

Declarations

Availability of data and material

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

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors are informed and agree to publish

Conflict of interest

There are no financial or other relations that could lead to a conflict of interest.

Funding

Provincial Science and Technology Plan Project of Hebei Province (17397765D).

Authors' contributions

Erhei Dai conceived and designed the study. Literature search: Bo Zhu,Xiuli Chen. Data extraction: Bo Zhu, Xiuli Chen, Fumin Feng. Data analysis: Bo Zhu. Drafting manuscript: Bo Zhu. ErHei Dai, Fumin Feng reviewed and edited the manuscript. All authors read and approved the manuscript.

Acknowledgements

Acknowledge anyone who contributed towards the article who does not meet the criteria for authorship including anyone who provided professional writing services or materials.

Referances

1. Ganem D, Prince AM. Hepatitis B virus infection--natural history and clinical consequences. The New England journal of medicine. 2004;350(11):1118-29.
2. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet (London, England). 2015;386(10003):1546-55.
3. World Health Organization Hepatitis B Fact Sheet. (accessed on 19 July ,2019);.
4. Stevens CE, Toy P, Kamili S, Taylor PE, Tong MJ, Xia GL, et al. Eradicating hepatitis B virus: The critical role of preventing perinatal transmission. Biologicals : journal of the International Association of Biological Standardization. 2017;50:3-19.
5. Yin Y, Wu L, Zhang J, Zhou J, Zhang P, Hou H. Identification of risk factors associated with immunoprophylaxis failure to prevent the vertical transmission of hepatitis B virus. The Journal of infection. 2013;66(5):447-52.
6. Liang X, Bi S, Yang W, Wang L, Cui G, Cui F, et al. Epidemiological serosurvey of hepatitis B in China--declining HBV prevalence due to hepatitis B vaccination. Vaccine. 2009;27(47):6550-7.
7. Zhang L, Gui XE, Teter C, Zhong H, Pang Z, Ding L, et al. Effects of hepatitis B immunization on prevention of mother-to-infant transmission of hepatitis B virus and on the immune response of infants towards hepatitis B vaccine. Vaccine. 2014;32(46):6091-7.
8. Schillie S, Vellozzi C, Reingold A, Harris A, Haber P, Ward JW, et al. Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports. 2018;67(1):1-31.

9. Liu C, Li H, Gao L, Li F, Liang X, Yang K. Hepatitis B immunisation leads to the decline of hepatitis B virus prevalence in Gansu province, China. Aust N Z J Public Health. 2011;35(1):91-2.
10. Wiseman E, Fraser MA, Holden S, Glass A, Kidson BL, Heron LG, et al. Perinatal transmission of hepatitis B virus: an Australian experience. The Medical journal of Australia. 2009;190(9):489-92.
11. Zou H, Chen Y, Duan Z, Zhang H, Pan C. Virologic factors associated with failure to passive-active immunoprophylaxis in infants born to HBsAg-positive mothers. Journal of viral hepatitis. 2012;19(2):e18-25.
12. Liu SL, Dong Y, Zhang L, Li MW, Wo JE, Lu LW, et al. Influence of HBV gene heterogeneity on the failure of immunization with HBV vaccines in eastern China. Archives of virology. 2009;154(3):437-43.
13. Kang W, Li Q, Shen L, Zhang L, Tian Z, Xu L, et al. Risk factors related to the failure of prevention of hepatitis B virus Mother-to-Child transmission in Yunnan, China. Vaccine. 2017;35(4):605-9.
14. Liu CP, Zeng YL, Zhou M, Chen LL, Hu R, Wang L, et al. Factors associated with mother-to-child transmission of hepatitis B virus despite immunoprophylaxis. Internal medicine (Tokyo, Japan). 2015;54(7):711-6.
15. Zhang L, Gui X, Wang B, Ji H, Yisilafu R, Li F, et al. A study of immunoprophylaxis failure and risk factors of hepatitis B virus mother-to-infant transmission. Eur J Pediatr. 2014;173(9):1161-8.
16. Park JS, Pan C. Current recommendations of managing HBV infection in preconception or pregnancy. Front Med. 2014;8(2):158-65.
17. Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. The lancet Gastroenterology & hepatology. 2018;3(6):383-403.
18. Li XM, Yang YB, Hou HY, Shi ZJ, Shen HM, Teng BQ, et al. Interruption of HBV intrauterine transmission: a clinical study. World J Gastroenterol. 2003;9(7):1501-3.
19. Xu WM, Cui YT, Wang L, Yang H, Liang ZQ, Li XM, et al. Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multicentre, randomized, double-blind, placebo-controlled study. Journal of viral hepatitis. 2009;16(2):94-103.
20. Pan CQ, Yi W, Liu M, Wan G, Hu YH, Zhou MF. Lamivudine therapy during the second vs the third trimester for preventing transmission of chronic hepatitis B. Journal of viral hepatitis. 2017;24(3):246-52.
21. 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. Journal of viral hepatitis. 2003;10(4):294-7.
22. Yu M, Jiang Q, Ji Y, Jiang H, Wu K, Ju L, et al. The efficacy and safety of antiviral therapy with lamivudine to stop the vertical transmission of hepatitis B virus. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology. 2012;31(9):2211-8.
23. 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. China Prac Med. 2007;2(13):14-6.
24. Feng HF, Zhang SF. Effect on Interrupton of Hepatitis B virus vertical Transmission by Lam ivudne. Chinese Journal of Practical Pediatrics. 2007;22(13):1019-20.
25. Yang S, Liu M, Wang L. Effect of high viral hepatitis B virus DNA loads on vertical transmission of hepatitis B virus in late-pregnant women. Chin J Obstet Gynecol. 2008;5(43):329-31.
26. Jiang HX, Han GR, Wang CM, Ji Y. Maternal-fetal outcomes of lamivudine treatment administered during late pregnancy to highly viremic mothers with HBeAg+ chronic hepatitis B. Chin J Hepatol. 2012;12(20):888-91.
27. Zhang H, Pan CQ, Pang Q, Tian R, Yan M, Liu X. Telbivudine or lamivudine use in late pregnancy safely reduces perinatal transmission of hepatitis B virus in real-life practice. Hepatology (Baltimore, Md). 2014;60(2):468-76.
28. Han GR, Cao MK, Zhao W, Jiang HX, Wang CM, Bai SF, et al. A prospective and open-label study for the efficacy and safety of telbivudine in pregnancy for the prevention of perinatal transmission of hepatitis B virus infection. J Hepatol. 2011;55(6):1215-21.
29. Yu MM, Jiang Q, Ji Y, Wu KH, Ju LL, Tang X, et al. Comparison of telbivudine versus lamivudine in interrupting perinatal transmission of hepatitis B virus. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. 2014;61(1):55-60.
30. Sheng Q, Ding Y, Li B, Han C, Li Y, Zhang C, et al. Efficacy and safety of nucleos(t)ide analogues to prevent hepatitis B virus mother-to-child transmission in pregnant women with high viremia: real life practice from China. Int J Med Sci. 2018;15(8):796-801.
31. Liu Y, Wang M, Yao S, Yuan J, Lu J, Li H, et al. Efficacy and safety of telbivudine in different trimesters of pregnancy with high viremia for interrupting perinatal transmission of hepatitis B virus. Hepatology research : the official journal of the Japan Society of Hepatology. 2016;46(3):E181-8.
32. Han GR, Jiang HX, Yue X, Ding Y, Wang CM, Wang GJ, et al. Efficacy and safety of telbivudine treatment: an open-label, prospective study in pregnant women for the prevention of perinatal transmission of hepatitis B virus infection. Journal of viral hepatitis. 2015;22(9):754-62.
33. Yi W, Li MH, Xie Y, Wu J, Hu YH, Zhang D, et al. Prospective cohort study on the efficacy and safety of telbivudine used throughout pregnancy in blocking mother-to-child transmission of hepatitis B virus. Journal of viral hepatitis. 2017:49-56.
34. Pan CQ, Han GR, Jiang HX, Zhao W, Cao MK, Wang CM, et al. Telbivudine prevents vertical transmission from HBeAg-positive women with chronic hepatitis B. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2012;10(5):520-6.
35. Wu Q, Huang H, Sun X, Pan M, He Y, Tan S, et al. Telbivudine prevents vertical transmission of hepatitis B virus from women with high viral loads: a prospective long-term study. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2015;13(6):1170-6.

36. Zhang LJ, Wang L. Blocking intrauterine infection by telbivudine in pregnant chronic hepatitis B patients. Chin J Hepatol. 2009;8(17):561-63.
37. Zhao DB, Liao XQ, Peng GJ, Liu J, Lin CS. Analysis of the efficacy of telbivudine combined with hepatitis B vaccine and hepatitis B immunoglobulin in blocking mother-to-child transmission of hepatitis B virus. Chin J Mod Drug Appl. 2010;17(4):37-8.
38. Zhang YF, Hu YH. Efficacy and safety of telbivudin in preventing mother-to-infant HBV transmission. ADRJ. 2010;3(12):157-59.
39. Zeng YM, Zhang SQ, Lou GQ, Chen J, Shi JP, Liu SHR, et al. Clinical study on preventing babby infections in uterine from hepatitis B virus with telbivudine. Chinese Journal of Clinical Pharmacology and Therapeutics. 2010;4(15):443-5.
40. Yao ZC, Chen MC, Liao WY, Zhang YP, Wu L, Li LY. The efficacy and safety of telbivudine in blocking intrauterine hepatitis B viral transmission. J Clin Hepatol. 2011;14(4):259-61.
41. Zeng J, Zheng C, Li H. Effectiveness of tenofovir or telbivudine in preventing HBV vertical transmission for pregnancy. Medicine. 2019;98(14):e15092.
42. Shen GJ, Yue T, Tao YL, Huang J, Zhang KK, Xia ZZ, et al. The efficacy and safety of tenofovir in blocking mother-to-child transmission of HBV in late pregnancy. Chinese Hepatology,. 2019;1(24):63-5.
43. Xiao X, Gao X. The effect of telbivudine and tenofovir in the third trimester of hepatitis B virus infected women. Matemal and Child Health Care of China. 2017;18(32):4567-70.
44. Wang YH, Sun L, Huang XJ, Li W, Zhao WJ. Efficacy and safety of tenofovir disoproxil on blocking mother-to-child transmission of HBV in pregnant women with HBV DNA high load in late pregnancy. Chinese Journal of Liver Diseases(Electronic Version). 2019;2(11):37-41.
45. Chen WJ, Song SR, He H, Liang Q. Blocking effect and safety of tenofovir and telbivudine during pregnancy on mother-to-child transmission of HBV. Shandong Medical Journal. 2017;22(57):73-5.
46. Samadi Kochaksaraei G, Castillo E, Osman M, Simmonds K, Scott AN, Oshiomogho JI, et al. Clinical course of 161 untreated and tenofovir-treated chronic hepatitis B pregnant patients in a low hepatitis B virus endemic region. Journal of viral hepatitis. 2016;23(1):15-22.
47. Pan CQ, Duan Z, Dai E, Zhang S, Han G, Wang Y, et al. Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load. The New England journal of medicine. 2016;374(24):2324-34.
48. Chang KC, Chang MH, Lee CN, Chang CH, Wu JF, Ni YH, et al. Decreased neonatal hepatitis B virus (HBV) viremia by maternal tenofovir treatment predicts reduced chronic HBV infection in children born to highly viremic mothers. Aliment Pharmacol Ther. 2019;50(3):306-16.
49. Lin Y, Liu Y, Ding G, Touqui L, Wang W, Xu N, et al. Efficacy of tenofovir in preventing perinatal transmission of HBV infection in pregnant women with high viral loads. Sci Rep. 2018;8(1):15514.
50. Celen MK, Mert D, Ay M, Dal T, Kaya S, Yildirim N, et al. Efficacy and safety of tenofovir disoproxil fumarate in pregnancy for the prevention of vertical transmission of HBV infection. World J Gastroenterol. 2013;19(48):9377-82.
51. Chen HL, Lee CN, Chang CH, Ni YH, Shyu MK, Chen SM, et al. Efficacy of maternal tenofovir disoproxil fumarate in interrupting mother-to-infant transmission of hepatitis B virus. Hepatology (Baltimore, Md). 2015;62(2):375-86.
52. Greenup AJ, Tan PK, Nguyen V, Glass A, Davison S, Chatterjee U, et al. Efficacy and safety of tenofovir disoproxil fumarate in pregnancy to prevent perinatal transmission of hepatitis B virus. J Hepatol. 2014;61(3):502-7.
53. Navabakhsh B, Mehrabi N, Estakhri A, Mohamadnejad M, Poustchi H. Hepatitis B Virus Infection during Pregnancy: Transmission and Prevention. Middle East journal of digestive diseases. 2011;3(2):92-102.
54. Alter MJ. Epidemiology of hepatitis B in Europe and worldwide. J Hepatol. 2003:S64-9.
55. Beasley RP, Hwang LY, Lee GC, Lan CC, Roan CH, Huang FY, et al. Prevention of perinatally transmitted hepatitis B virus infections with hepatitis B immune globulin and hepatitis B vaccine. Lancet (London, England). 1983;2(8359):1099-102.
56. Roznovsky L, Orsagova I, Kloudova A, Tvrdik J, Kabieszova L, Lochman I, et al. Long-term protection against hepatitis B after newborn vaccination: 20-year follow-up. Infection. 2010;38(5):395-400.
57. Kubo A, Shlager L, Marks AR, Lakritz D, Beaumont C, Gabellini K, et al. Prevention of vertical transmission of hepatitis B: an observational study. Ann Intern Med. 2014;160(12):828-35.
58. Yang L, Yang X, Kong X, Cao Z, Zhang Y, Hu Y, et al. Covariation Analysis of Serumal and Urinary Metabolites Suggests Aberrant Glycine and Fatty Acid Metabolism in Chronic Hepatitis B. PLoS One. 2016;11(5):e0156166.
59. Jonas MM. Hepatitis B and pregnancy: an underestimated issue. Liver international : official journal of the International Association for the Study of the Liver. 2009:133-9.
60. Ding Y, Sheng Q, Ma L, Dou X. Chronic HBV infection among pregnant women and their infants in Shenyang, China. Virol J. 2013;10:17.
61. Yi W, Pan CQ, Hao J, Hu Y, Liu M, Li L, et al. Risk of vertical transmission of hepatitis B after amniocentesis in HBs antigen-positive mothers. J Hepatol. 2014;60(3):523-9.
62. Pawlowska M, Pniewska A, Pilarczyk M, Kozielewicz D, Domagalski K. Prophylaxis of vertical HBV infection. Expert Opin Drug Saf. 2016;15(10):1361-8.
63. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67(2):370-98.
64. Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. AASLD guidelines for treatment of chronic hepatitis B. Hepatology (Baltimore, Md). 2016;63(1):261-83.
65. Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int. 2016;10(1):1-98.
66. Hoofnagle JH, di Bisceglie AM. The treatment of chronic viral hepatitis. The New England journal of medicine. 1997;336(5):347-56.
67. Zoulim F. A preliminary benefit-risk assessment of lamivudine for the treatment of chronic hepatitis B virus infection. Drug Saf. 2002;25(7):497-510.

68. But DY, Yuen MF, Fung J, Lai CL. Safety evaluation of telbivudine. Expert Opin Drug Saf. 2010;9(5):821-9.
69. Lai CL, Gane E, Liaw YF, Hsu CW, Thongsawat S, Wang Y, et al. Telbivudine versus lamivudine in patients with chronic hepatitis B. The New England journal of medicine. 2007;357(25):2576-88.
70. Buti M, Tsai N, Petersen J, Flisiak R, Gurel S, Krastev Z, et al. Seven-year efficacy and safety of treatment with tenofovir disoproxil fumarate for chronic hepatitis B virus infection. Digestive diseases and sciences. 2015;60(5):1457-64.
71. Hyun MH, Lee YS, Kim JH, Je JH, Yoo YJ, Yeon JE, et al. Systematic review with meta-analysis: the efficacy and safety of tenofovir to prevent mother-to-child transmission of hepatitis B virus. Aliment Pharmacol Ther. 2017;45(12):1493-505.
72. Price H, Dunn D, Pillay D, Bani-Sadr F, de Vries-Sluijs T, Jain MK, et al. Suppression of HBV by tenofovir in HBV/HIV coinfected patients: a systematic review and meta-analysis. PLoS One. 2013;8(7):e68152.
73. Pan CQ, Mi LJ, Bunchorntavakul C, Karsdon J, Huang WM, Singhvi G, et al. Tenofovir disoproxil fumarate for prevention of vertical transmission of hepatitis B virus infection by highly viremic pregnant women: a case series. Digestive diseases and sciences. 2012;57(9):2423-9.
74. Deng M, Zhou X, Gao S, Yang SG, Wang B, Chen HZ, et al. The effects of telbivudine in late pregnancy to prevent intrauterine transmission of the hepatitis B virus: a systematic review and meta-analysis. Virol J. 2012;9:185.
75. Brown RS, McMahon BJ, Lok AS, Wong JB, Ahmed AT, Mouchli MA, et al. Antiviral therapy in chronic hepatitis B viral infection during pregnancy: A systematic review and meta-analysis. Hepatology (Baltimore, Md). 2016;63(1):319-33.

Figures

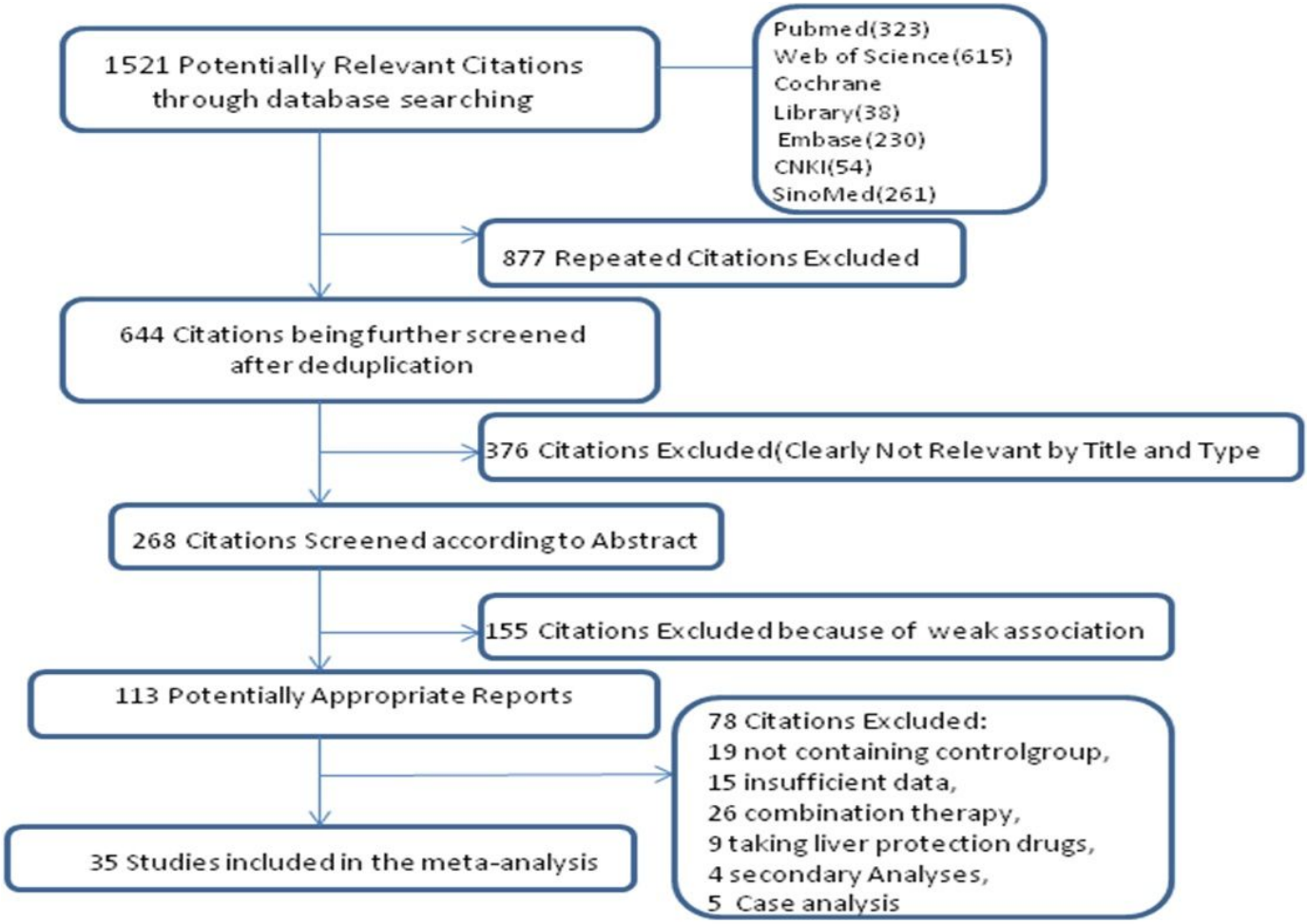

Figure 1

The PRISMA flow of this study

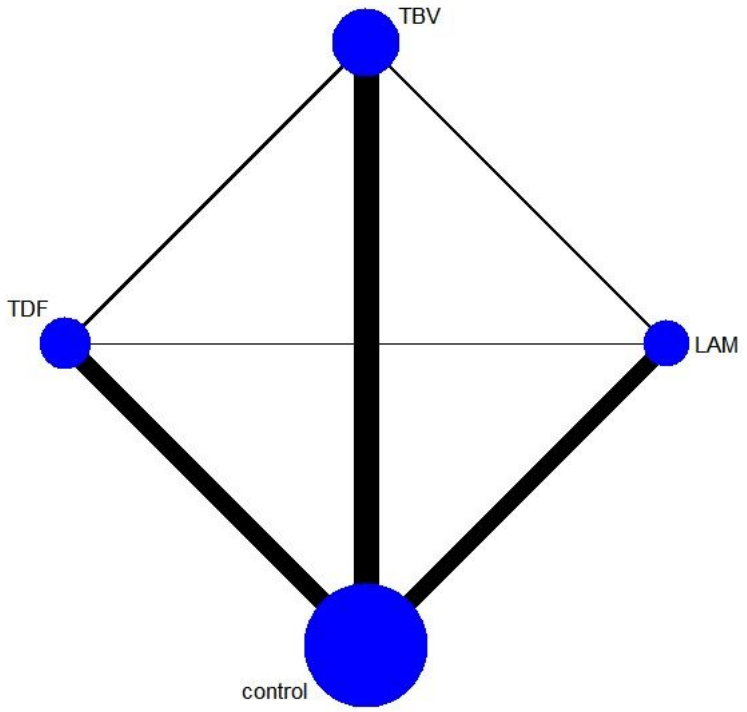

Figure 2

Evidence network of eligible studies for network meta-analysis

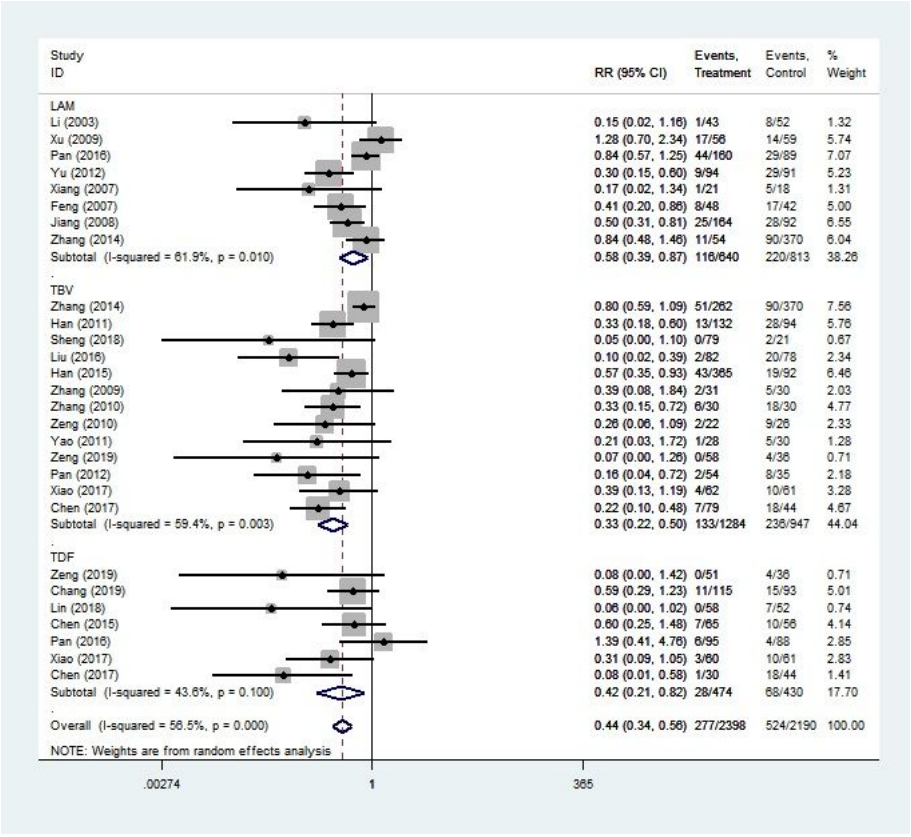

Figure 3

Forest plots of Infant HBsAg positivity at birth

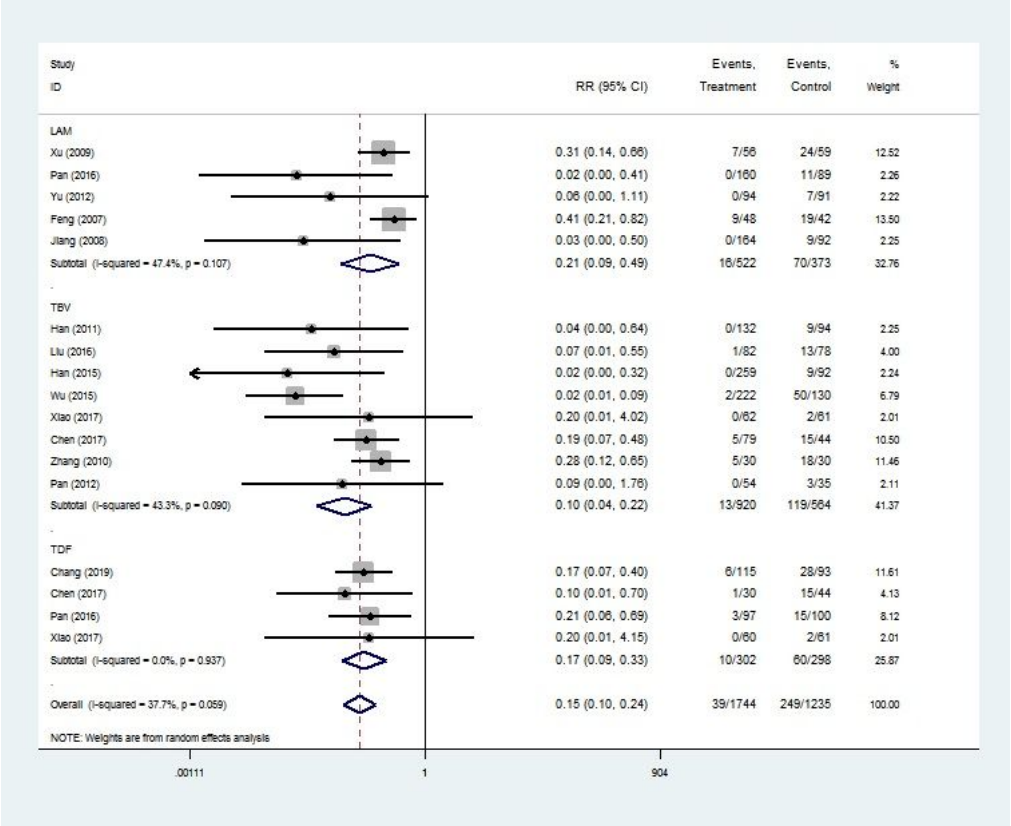

Figure 4

Forest plots of Infant HBsAg positivity at 6-12 months

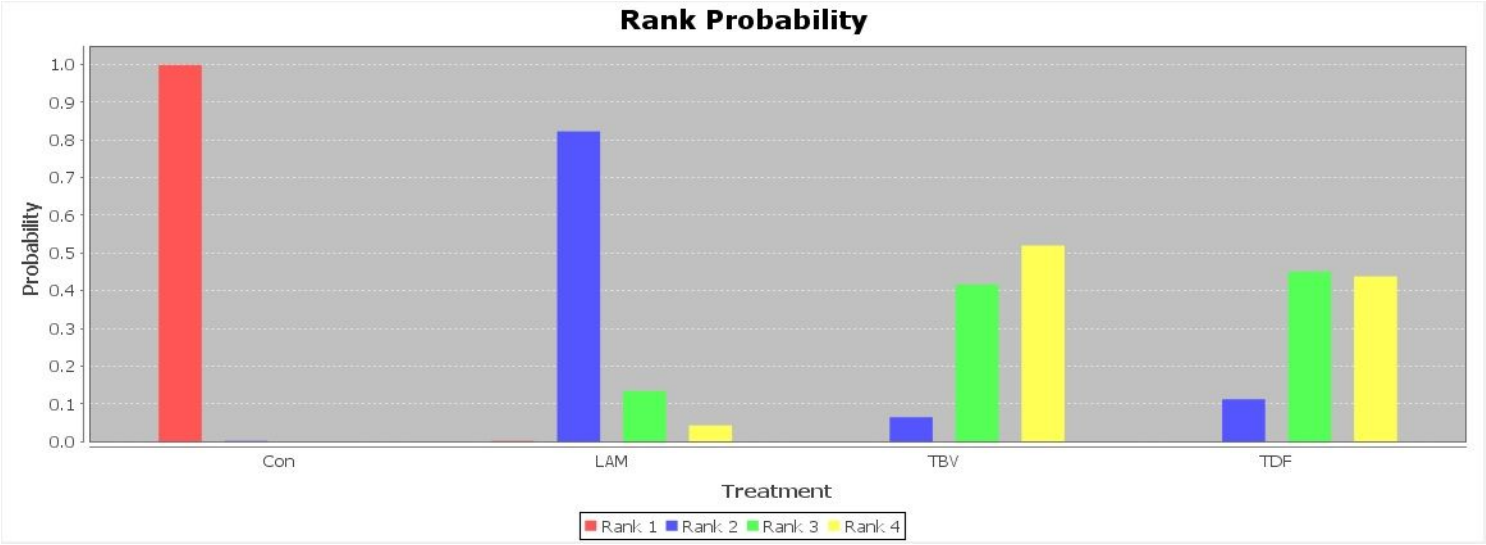

Figure 5

Possible Ranking of Three Antiviral Drugs to Block Mother-to-Child Transmission of HBV

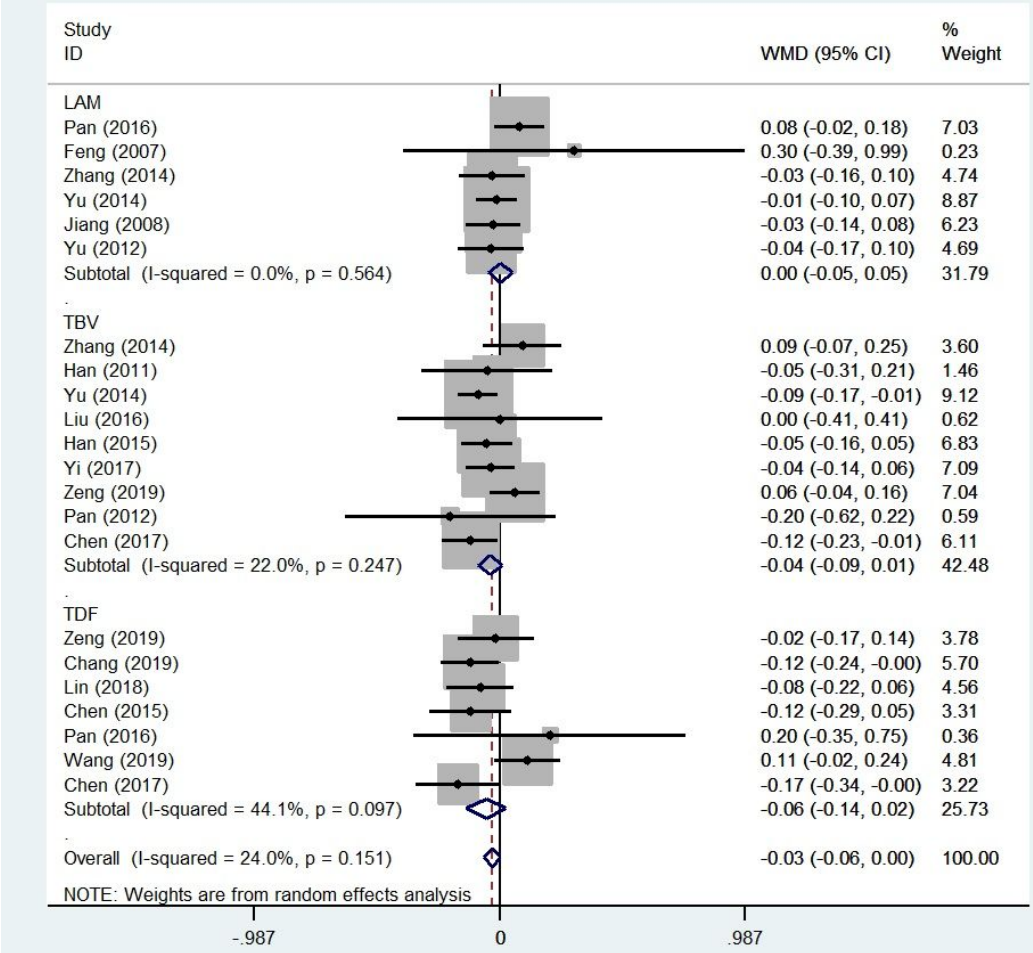

Figure 6

Forest plots of the weight of newborns

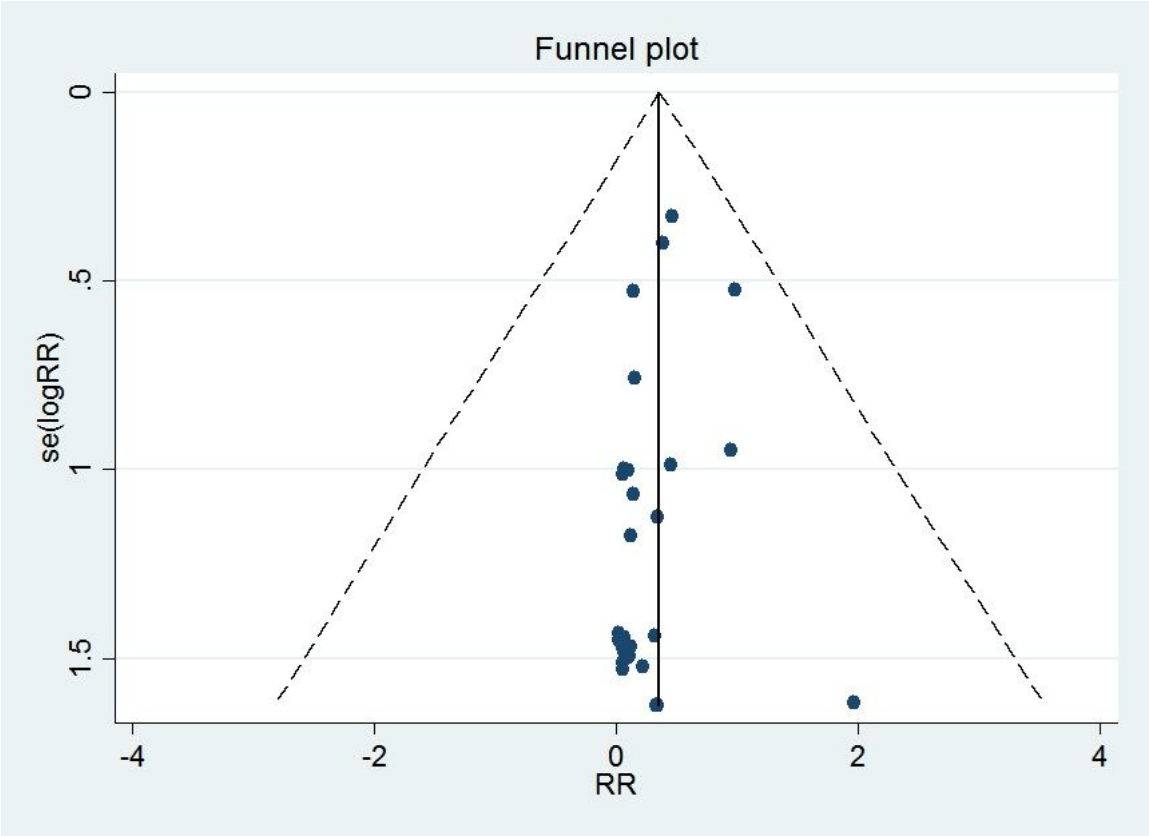

Figure 7

Funnel plot of MTCT

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementary.doc
- SupplementaryMaterialmydata.xls