

Lamivudine's efficacy and safety in preventing mother-to-child transmission of hepatitis B: A meta-analysis

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ABSTRACT

Background/Aims: Mother-to-child transmission (MTCT) is a common transmission mode of hepatitis B virus (HBV). It has been shown that the infection may occur in some infants despite the use of immunoprophylaxis, and many studies have demonstrated the efficacy of antivirals such as lamivudine to reduce such events.

Materials and Methods: A meta-analysis was conducted concerning the efficacy and safety of lamivudine during pregnancy, in the prevention of vertical transmission of HBV infection. Studies were identified by searching various databases up to January 2016 for variations of the following phrase: "lamivudine AND (pregnancy or pregnant) AND (HBV or hepatitis)." Subjects who had received lamivudine were included in the case group, and those who had not were included in the control group.

Results: Our search identified a total number of 881 citations, of which 25 studies (with a total number of 2,667 pregnant women) were included in the meta-analysis. The analysis showed a significant difference between the seropositive HBsAg infants from the case and control groups (RR= 16.97, 95% confidence interval 8.36-34.45), which is the most critical factor in determining the MTCT of HBV. No significant difference was reported between the prevalence of side effects in the case and control groups.

Conclusion: This meta-analysis strongly suggests the use of lamivudine in the prevention of HBV vertical transmission in carrier pregnant women with the HBV DNA levels greater than 10^6 copies/mL. And for women with the HBV viral loads lower than 10^6 copies/mL, we suggest clinicians to examine the use of lamivudine on a case-to-case basis, noting that lamivudine seems to be a safe drug for the mother and the fetus.

Keywords: Lamivudine, hepatitis B, pregnancy, mother-to-child transmission, anti-retroviral agents, fetomaternal infection

INTRODUCTION

Hepatitis B virus (HBV) infection is a major global health issue. It is estimated that more than 240 million individuals are chronically infected with HBV worldwide (1). Mother-to-child transmission (MTCT), which usually occurs perinatally and in rare cases in utero, is a common mode of HBV's transmission, especially in endemic countries (2,3).

Chronic hepatitis B (CHB) arises in up to 90% of infants who were infected perinatally, and it may eventually lead to serious complications that may happen as soon as adolescence, such as liver failure, cirrhosis, and hepatocellular carcinoma (3).

Immunoprophylaxis with hepatitis B immunoglobulin (HBIG) administered within 12 hours of birth and a series of three doses of hepatitis B vaccination can

prevent perinatal HBV transmission in 90%-95% of infants born to HBsAg-positive mothers. However, it has been shown that the infection may occur in 5%-10% of infants despite the use of immunoprophylaxis (3-5); the main risk factors of prevention failure are the maternal high viral load and the HBeAg positivity (5-7). Therefore, the administration of oral antiviral drugs to decrease the maternal serum HBV DNA levels is expected to reduce the rate of perinatal HBV infection in newborns (8).

Many studies have shown the efficacy of antiviral therapy to reduce the MTCT of HBV infection in pregnant women with the high viral load (8,9). Lamivudine is a nucleoside analog antiviral drug with a record of safe use in pregnancy that effectively decreased the MTCT of HBV in several clinical trials with no increased adverse outcomes (10,11).

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"See Editorial Comment 1-2"

In this study, we conducted a systematic review and meta-analysis of clinical trials and cohort studies up to January 2016 to evaluate lamivudine's efficacy and safety on the prevention of MTCT of HBV. Three meta-analyses have already been conducted on this subject (9-11) of which two are outdated (2010 and 2011) considering the vast amount of studies performed after their publication, and the third meta-analysis is conducted about the efficacy of all used antivirals, not exclusively lamivudine.

MATERIALS AND METHODS

Search strategy and study selection

An online literature search was performed to identify relevant English articles pertaining the efficacy of lamivudine in the prevention of vertical transmission of Hepatitis B from mother-to-child. Publications and abstracts up to January 2016 were searched and obtained from the following databases: PubMed, EMBASE, Scopus, Web of Science, The Cochrane Library, Irandoc, IRCT, Iran medex, ClinicalTrials.gov, African Index Medicus, European Union Clinical Trials Registry, Google Scholar, Proquest, Biosis Citation Index, HSRProj (Health Services Research Projects in Progress), Open Grey, AIHW, CogPrints, OALster (WorldCat), Science.gov, and OpenDoar.

Different variations of the following phrase were searched mainly in the abstracts: "lamivudine AND (pregnancy or pregnant) AND (HBV or hepatitis)". Moreover, cited articles in the selected studies were manually examined to prevent any omission of related studies.

Relevant articles that had one or more of the following criteria were excluded from this analysis: animal studies, case reports, co-infection of HBV and HIV, combination therapy with other antivirals, review articles, and letters to editors.

Data extraction

Titles and abstracts of all potentially relevant articles were reviewed independently by two authors (P.KH. and R.J), and relevant articles were included in the analysis; disagreements were reconciled by consensus or by a third reviewer (M.G.).

The same two authors performed data extraction, and in case of any disagreements, reconciliation was made by consensus or by a third reviewer. Data were extracted from full texts of the English studies, and also from the abstract of non-English studies as well as the abstract of studies that had not been published as a finished proj-

ect yet. To obtain further data, we tried to contact corresponding authors of all the studies who did not have a full text in English or did not have a full text at all.

The following data of case and control groups were extracted and indexed in an Excel sheet from each eligible study: name of the first author, year of publication, type of study, country, blinding method, sample size, number of newborns, mother's mean age, intervention on mothers, intervention on newborns, maternal serum HBV DNA level before intervention and before delivery, ALT changes, HBsAg-positive newborns and infants, and adverse events in newborns (still birth, premature rupture of membrane, low birth weight, cerebral palsy, and apparent deformities).

Infancy was defined as the age greater than 28 days.

Pregnant women who had received lamivudine were included in the case group, and those who had not received lamivudine were included in the control group. Table 1 demonstrates the interventions performed on mothers and newborns of both groups.

The analysis was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

Statistical analysis

Maternal HBV DNA level changes during lamivudine treatment between the case and control groups and the relative risk were combined by the "metan" command. Also, we used the "metaprop" command for the prevalence of abnormal ALT levels in the case group of each study (12). Statistical tests of heterogeneity among studies were carried out using the Q test ($P < 0.10$ indicated a statistically significant heterogeneity) and the I-squared statistics. If heterogeneity was confirmed, the "Fixed Effect Method" was used for a combination of effects, and if it was not confirmed, the "Random Effect Method" was used. In this study, we also used a funnel plot to investigate publication bias and forest plot for showing the study effect and 95% confidence interval (CI). The analyses were performed using the 11th version of Stata software.

RESULTS

A total number of 881 citations were identified via our search in the previously mentioned databases. After processing the studies, which is described in Figure 1, 25 studies (13-37) were included in this meta-analysis. The included studies were published between 2003 and 2015 and enrolled a total number of 2,667 HBV-infected pregnant

Table 1. General information of included studies

| First author, year | Accessed article | Country | Sample Size (Mothers) (N) | | Blinding | Mothers' mean (± SD) / median age (Years) | | Intervention on mothers | | Intervention on newborns | | Duration of treatment in cases | |
|--------------------|---------------------|-------------|---------------------------|---------------|----------|---|---------------|-------------------------|---------------|--|--|--|------------------------|
| | | | Case group | Control group | | Case group | Control group | Case group | Control group | Case group | Control group | Start | Discontinuation |
| Ayres, 2013 | Full-text | Australia | 21 | 5 | No | N/A | N/A | 100mg LMV qd | None | N/A | N/A | 32 nd GW | 2 weeks postpartum |
| Erturk, 2014 | Full-text | Turkey | 8 | No control | N/A | 26.5 | No control | 100mg LMV qd | No control | N/A | N/A | 28 th – 32 nd GW | After 8-12 weeks |
| Jackson, 2015 | Full-text | Ireland | 34 | 9 | N/A | 26 | N/A | 100-150 mg LMV qd | None | HBIG; 0.4 mL/kg + recombinant HBV vaccine | HBIG; 0.4 mL/kg + recombinant HBV vaccine | 32 nd GW | Delivery |
| Jiang, 2012 | Abstract | China | 164 | 92 | N/A | N/A | N/A | 100mg LMV qd | None | HBIG; 200 IU+ recombinant HBV vaccine (20 mug) | HBIG; 200 IU+ recombinant HBV vaccine (20 mug) | 2 nd or 3 rd trimester | N/A |
| Kose, 2011 | Full-text | Turkey | 7 | No control | N/A | 26.5 | No control | 100mg LMV qd | No control | N/A | N/A | 32 nd GW | After 8 weeks |
| Lawler, 2011 | Conference Abstract | Australia | 44 | 15 | N/A | N/A | N/A | N/A | None | N/A | N/A | 32 nd GW | After 50 days |
| Li, 2003 | Full-text | China | 43 | 52 | N/A | N/A | N/A | 100mg LMV qd | None | N/A | N/A | 28 th GW | 30 days after delivery |
| Min, 2008 | Abstract | China | 15 | No control | N/A | 29 | No control | 100mg LMV qd | No control | N/A | N/A | Before pregnancy | Delivery |
| Pan, 2011 | Conference Abstract | China | 164 | 92 | N/A | 27 | 26 | 100mg LMV qd | None | HBIG; 200 IU+ recombinant HBV vaccine (20 mug) | HBIG; 200 IU+ recombinant HBV vaccine (20 mug) | 2 nd or 3 rd trimester | 4 weeks postpartum |
| Pan, 2014 | Conference Abstract | China & USA | 94 | 89 | N/A | 27.4 | 27.2 | 100mg LMV qd | None | HBIG; 200 IU+ recombinant HBV vaccine (20 mug) | HBIG; 200 IU+ recombinant HBV vaccine (20 mug) | 3 rd trimester | After 11.63 weeks |
| Su, 2004 | Full-text | China | 38 | 10 | N/A | N/A | N/A | 100mg LMV qd | None | HBIG; 200 IU+ recombinant HBV vaccine (20 mug) | HBIG; 200 IU+ recombinant HBV vaccine (20 mug) | Before pregnancy | N/A |
| Uchila, 2015 | Conference Abstract | Australia | 6 | No control | N/A | N/A | No control | 100mg LMV qd | No control | N/A | N/A | 3 rd trimester | N/A |
| Van Bang, 2015 | Full-text | Vietnam | 33 | No control | N/A | N/A | No control | 100mg LMV qd | No control | recombinant HBV vaccine (standard 4 doses) | N/A | 32 nd GW | 4 weeks postpartum |

Table 1. General information of included studies (Continued)

| Author, Year | Study Design | Country | n | Control | Intervention | Outcome | Follow-up | Notes | | | | | |
|-------------------|---------------------|---------------------|-----|------------|----------------|-------------|-------------|--------------|--------------|--|--|--|--------------------|
| Xu, 2009 | Full-text | China & Philippines | 89 | 61 | Double Blinded | 26 | 25 | 100mg LMV qd | None | 56 cases Received Vaccine + HBIG, 26 cases Received Vaccine only | Vaccine + HBIG | 32 nd GW | 4 weeks postpartum |
| Yang, 2008 | Abstract | China | 20 | 20 | Double Blinded | N/A | N/A | 100mg LMV qd | None | N/A | N/A | 28 th GW | Delivery |
| Xiaomoing, 2012 | Abstract | China | 57 | 66 | N/A | N/A | N/A | 100mg LMV qd | HBIG, 200 IU | HBIG; 200 IU+ recombinant HBV vaccine (20 mug) | HBIG; 200 IU+ recombinant HBV vaccine (20 mug) | 20 th – 26 th GW | Delivery |
| Yi, 2012 | Full-text | China | 72 | No control | N/A | 30.5±3.1 | No control | 100mg LMV qd | No control | HBIG; 200 IU+ Three doses of recombinant HBV vaccine (10 mug) | N/A pregnancy | Before or early | N/A |
| Han, 2005 | Abstract | China | 42 | No control | N/A | N/A | No control | 100mg LMV qd | No control | N/A | N/A | 28 th GW | N/A |
| Jiang, 2012 | Conference Abstract | China | 100 | 100 | N/A | N/A | N/A | 100mg LMV qd | HBIG, 200 IU | N/A | N/A | N/A | N/A |
| Tekin Koruk, 2015 | Full-text | Turkey | 20 | 54 | N/A | 28.1 | 28.7 | 100mg LMV qd | None | HBIG; 200 IU+ recombinant HBV vaccine (10 mug) | HBIG; 200 IU+ recombinant HBV vaccine (10 mug) | 22.2±8.5 GW | N/A |
| Yu, 2012 | Full-text | China | 94 | 91 | Double Blinded | 26.64± 4.17 | 25.78± 3.89 | 100mg LMV qd | None | HBIG; 200 IU+ recombinant HBV vaccine (10 mug) | HBIG; 200 IU+ recombinant HBV vaccine (20 mug) | 24 th – 32 nd GW | Delivery |
| Yu, 2014 | Full-text | China | 154 | 100 | N/A | 26.66± 3.48 | 26.11± 3.18 | 100mg LMV qd | HBIG, 200 IU | HBIG; 200 IU+ recombinant HBV vaccine (20 mug) | HBIG; 200 IU+ recombinant HBV vaccine (20 mug) | 8 th 32 nd GW | Delivery |
| Zhang, 2014 | Full-text | China | 53 | 363 | Open Label | 28.42± 7.12 | 28.97± 4.59 | 100mg LMV qd | None | HBIG; 200 IU+ recombinant HBV vaccine (10 mug) | HBIG; 200 IU+ recombinant HBV vaccine (10 mug) | 28 th – 32 nd GW | 4 weeks postpartum |
| Zonneveld, 2003 | Full-text | Netherlands | 8 | 24 | N/A | 20 | 23 | 150mg LMV qd | None | HBIG; 300 IU+ recombinant HBV vaccine (20 mug) | HBIG; 300 IU+ recombinant HBV vaccine (20 mug) | 34 th GW | Delivery |
| Yu, 2011 | Full-text | China | 14 | 30 | N/A | 27.68± 3.65 | 26.33± 3.24 | 100mg LMV qd | None | HBIG & Vaccine | HBIG & Vaccine | 3 rd trimester | Delivery |

LMV: Lamivudine; HBIG: Hepatitis B Immunoglobulin; HBV: Hepatitis B Virus; N/A: Not available; GW: Gestational Week

Table 2. Seropositivity of HBsAg and detectable loads of HBV DNA in newborns and infants

| | Case groups | | | | Control groups | | | | Relative Risk Comparison | | |
|---------------------------|---------------|--------------|--------|-------|----------------|--------------|--------|--------|--------------------------|--------|-------|
| | No of Studies | Total Events | 95% CI | | Total Samples | Total Events | 95% CI | | RR | 95% CI | |
| | | | L | U | | | L | U | | L | U |
| HBsAg Positive Newborns | 24 | 159 | 11.52% | 9.88% | 1380 | 278 | 21.38% | 26.35% | 2.07*** | 1.73 | 2.47 |
| HBsAg Positive Infants | 18 | 8 | 0.80% | 0.35% | 1001 | 134 | 11.49% | 15.86% | 16.97*** | 8.36 | 34.45 |
| HBV DNA Positive Newborns | 13 | 15 | 2.03% | 1.14% | 740 | 83 | 15.94% | 23.73% | 9.68*** | 5.66 | 16.56 |
| HBV DNA Positive Infants | 11 | 7 | 1.15% | 0.46% | 611 | 47 | 9.21% | 16.06% | 10.77*** | 4.92 | 23.58 |

*** p<0.0001; RR: Relative Risk

women of which 1,394 received lamivudine as an adjuvant therapy to the standard care to prevent MTCT of HBV. Table 1 summarizes the characteristics of the studies.

Infants’ outcome

The prevalence of seropositivity of HBsAg and detectable loads of HBV DNA in newborns and infants are demonstrated in Table 2, Figure 2, and Figure 3. The analysis shows a significant difference between the seropositive HBsAg infants from the case and control groups (relative risk [RR]=16.97, 95% CI 8.36-34.45). It is also apparent that there are significant differences between the two groups regarding the HBsAg in infants and HBV DNA in both infants and newborns.

A comparison of prevalence of side effects in the newborns was performed, which shows no significant difference between the two groups (p>0.1) (Table 3).

Mothers’ outcome

The analyses of changes in the maternal serum HBV DNA levels are shown in Figure 4 and Table 4. The efficacy of lamivudine in decreasing HBV DNA levels is calculated as -6.694 log10 IU/mL (95% CI, -7.836 to -5.552).

The meta-analysis combination for changes in the maternal serum ALT levels during lamivudine treatment is reported in Figure 5. It has been shown that ALT was

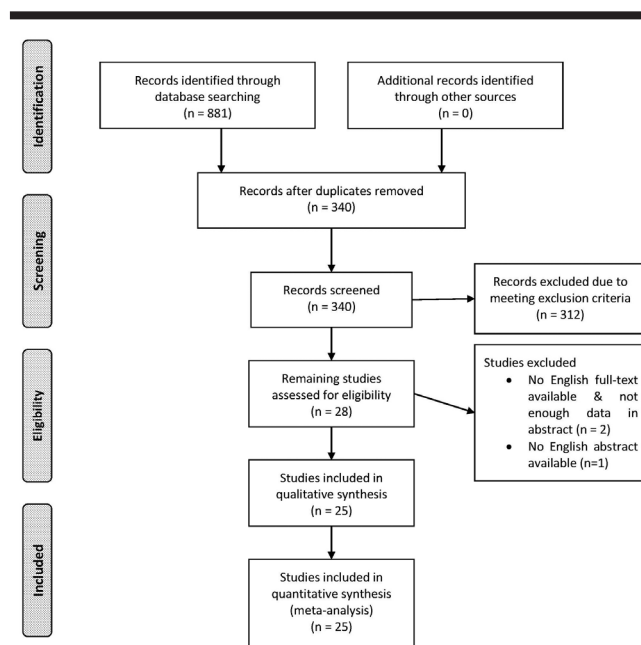


Figure 1. Flow chart of study recruitment and data selection

Table 3. The prevalence of side effects and relative risk comparison

| | Case | | | Control | | | Relative Risk Comparison | | | | |
|----------------------|---------------|--------------|---------------|---------------|--------------|---------------|--------------------------|-------|------|------|-------|
| | No of Studies | Total Events | Total Samples | No of Studies | Total Events | Total Samples | 95% CI | | RR | | |
| | | | | | | | L | U | | | |
| Still Birth | 18 | 2 | 1180 | 13 | 0 | 1149 | 0.02% | 0.61% | 0.34 | 0.04 | 3.29 |
| Low Birth Weight | 16 | 3 | 1130 | 11 | 5 | 756 | 0.27% | 0.77% | 2.49 | 0.6 | 10.39 |
| Cerebral Palsy | 17 | 0 | 1166 | 12 | 0 | 1119 | 0.00% | 0.32% | 1.04 | 0.07 | 16.64 |
| Apparent deformities | 17 | 3 | 1166 | 12 | 5 | 1119 | 0.26% | 0.75% | 1.74 | 0.42 | 7.25 |

RR: Relative Risk

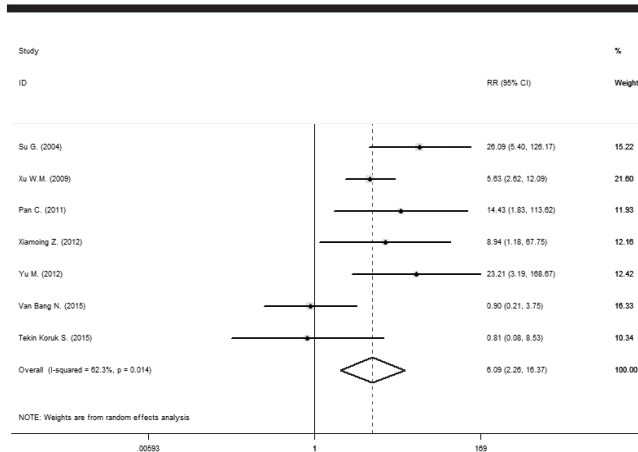


Figure 2. Forest plot for prevalence of detectable loads of HBV DNA in newborns

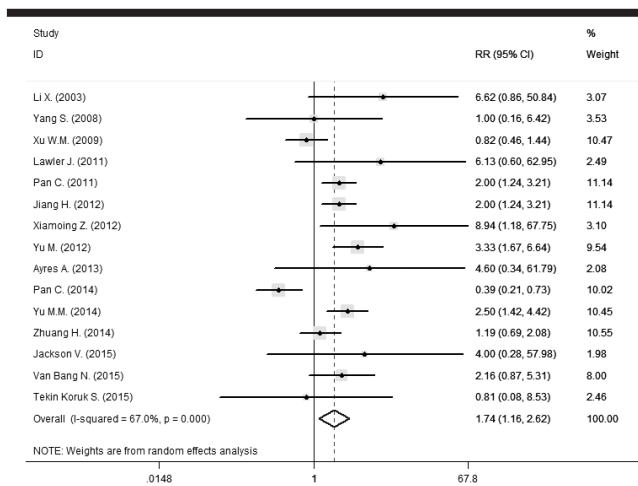


Figure 3. Forest plot for prevalence of HBS Ag positivity in newborns

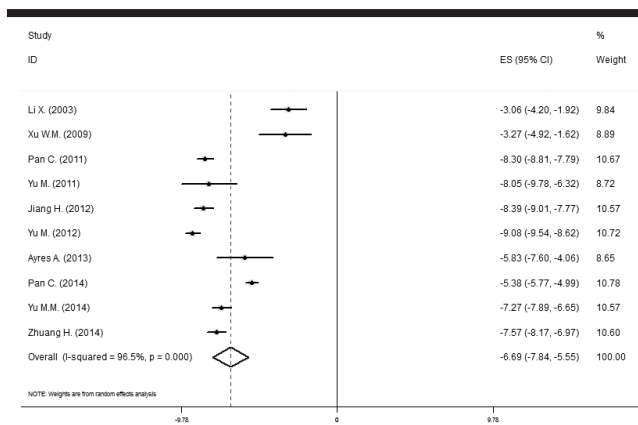


Figure 4. Forest plot for changes of maternal serum levels of HBV DNA during lamivudine treatment

Table 4. Pooled and study effect for changes in maternal serum levels of HBV DNA

| Author (Year) | Effect | 95 % Confidence Interval | |
|------------------|--------|--------------------------|--------|
| | | Lower | Upper |
| Li X. (2003) | -3.06 | -4.203 | -1.917 |
| Xu W.M. (2009) | -3.27 | -4.92 | -1.62 |
| Pan C. (2011) | -8.3 | -8.814 | -7.786 |
| Yu M. (2011) | -8.05 | -9.784 | -6.316 |
| Jiang H. (2012) | -8.39 | -9.014 | -7.766 |
| Yu M. (2012) | -9.08 | -9.54 | -8.62 |
| Ayres A. (2013) | -5.83 | -7.597 | -4.063 |
| Pan C. (2014) | -5.38 | -5.766 | -4.994 |
| Yu M.M. (2014) | -7.27 | -7.89 | -6.65 |
| Zhuang H. (2014) | -7.57 | -8.166 | -6.974 |
| Pooled | -6.694 | -7.836 | -5.552 |

Table 5. Pooled and study effect for prevalence of abnormal ALT levels

| Author (Year) | Effect | 95 % Confidence Interval | |
|--------------------|--------|--------------------------|--------|
| | | Lower | Upper |
| Zonneveld M.(2003) | 0.00% | 0.00% | 37.00% |
| Su G.(2004) | 26.00% | 13.00% | 43.00% |
| Min L.(2008) | 0.00% | 0.00% | 22.00% |
| Xu W.M.(2009) | 25.00% | 16.00% | 35.00% |
| Kose S.(2011) | 0.00% | 0.00% | 41.00% |
| Pan C.(2011) | 12.00% | 7.00% | 17.00% |
| Yu M.(2011) | 50.00% | 23.00% | 77.00% |
| Jiang H.(2012) | 10.00% | 6.00% | 15.00% |
| Xiamoing Z.(2012) | 0.00% | 0.00% | 6.00% |
| Yi W.(2012) | 22.00% | 13.00% | 34.00% |
| Yu M.(2012) | 9.00% | 4.00% | 16.00% |
| Erturk A.(2014) | 38.00% | 9.00% | 76.00% |
| Pan C.(2014) | 23.00% | 15.00% | 33.00% |
| Yu M.M.(2014) | 21.00% | 15.00% | 28.00% |
| Zhuang H.(2014) | 13.00% | 5.00% | 25.00% |
| Total | 12% | 7% | 18% |

decreased -84.52 IU/L (95% CI, -163.949 to -5.091) during lamivudine treatment. In this forest plot, the ALT normalization considered was taken as the end-point.

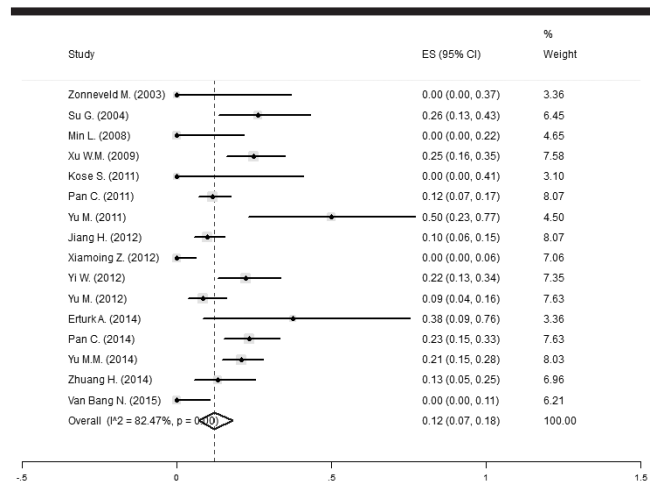


Figure 5. Forest plot for changes of maternal serum ALT levels during lamivudine treatment, with ALT normalization considered as the end-point

Table 5 contains the data regarding the prevalence of abnormal ALT levels. The ALT abnormality prevalence overlay was 12% (95% CI, 7% to 18%) during lamivudine treatment.

DISCUSSION

This meta-analysis included 25 RCTs and cohort studies published either in full text or as posters up to January 2016. Our review showed that the prenatal use of lamivudine is an effective way to lower the serum viral load of HBV and thus lower the risk of its vertical transmission to the newborn. Also, our analysis shows that lamivudine's efficacy is superior to either no treatment or the HBIg treatment. Moreover, our results showed that lamivudine is a safe drug to use in the third-trimester of pregnancy, as no significant higher rates of adverse events were observed with the use of lamivudine, including stillbirth, low birth weight, CP, and fetal deformities.

Three meta-analyses have already been conducted on the efficacy of lamivudine on the prevention of MTCT of HBV. In the studies performed by Shi et al. (10) and Han et al. (11), only 10 and 15 studies were included, respectively; that is because the majority of the studies on this subject were performed after publication of the mentioned reviews. Moreover, in a recent meta-analysis conducted by Brown and colleagues (9), all antivirals used in pregnant women with HBV were studied, and the focus was not on lamivudine, which is the most used drug from this category. Regarding lamivudine's safety, the findings of all three reviews were consistent with our results. However, respecting the efficacy, the review by Shi et al. (10)

showed no significant difference between the HBIG and lamivudine, while the other two reviews did; this inconsistency was most probably due to the insufficient number of included studies.

The MTCT can be designated by either serum HBsAg/HBeAg or the HBV DNA of newborns or infants; among these, HBsAg is believed to be more reliable and is more widely used. A reason is that the HBV DNA levels may be undetectable despite a positive HBsAg, especially in asymptomatic carriers (21,23,25). Thus, it is recommended to follow the infants of the HBV-carrier mothers for 6-12 months serially.

The AASLD guideline on the CHB management states that lamivudine's pregnancy safety category is C. (38) Since our review showed no significantly higher incidence of the analyzed pregnancy complications (i.e., stillbirth, low birth weight, cerebral palsy, apparent deformities) among mothers who received lamivudine in comparison to those who did not, it can be assumed that lamivudine is a safe drug for HBV-carrier mothers in the third-trimester. Although, it should be noted that the vast majority of included studies used lamivudine in the third-trimester, which has the lowest risk of adverse events on the fetus. Thus, it cannot be concluded that lamivudine's use is safe throughout the pregnancy.

Our study had some potential limitations, of which the most important one was a limited access to data from non-English literature. Not only three related studies were excluded from this analysis as one of them did not have an English abstract, and the other two did not include vital data, necessary for this analysis (including the rate of MTCT), but also five of the included studies were published in non-English languages, and we just had access to their abstracts; although the data required for analysis were included in their abstracts, we cannot say for sure what we may have missed in the full text. To control this limitation, we tried to contact the corresponding authors of the mentioned studies to seek more data (as well as authors of unpublished works that were presented as conference posters). Another important limitation of our study was not analyzing maternal seropositivity of HBsAg and HBeAg, as most of the included studies did not mention these variables. In addition to maternal HBV DNA levels, seropositivity of the mentioned antigens may be valuable in determining treatment strategies for pregnant HBV carriers; we suggest researchers to examine this theory further.

At the moment, the AASLD guideline suggests antiviral treatment (lamivudine, telbivudine, and tenofovir) for pregnant women with the HBV DNA levels greater than

10^6 copies/mL (200,000 IU/mL), but this is not "strongly" recommended, and it has been stated that the quality/certainty of evidence is low (38). However, our meta-analysis strongly suggests the use of lamivudine for the prevention of MTCT of HBV in carrier pregnant women with HBV DNA levels greater than 10^6 copies/mL; and for women with HBV, viral loads less than 10^6 copies/mL, we suggest clinicians to examine the use of lamivudine on a case-by-case basis, keeping in mind that lamivudine seems to be a safe drug both for the mother and the fetus.

Ethics Committee Approval: Ethics committee approval not received for this study as there are no human or animal subjects directly recruited.

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - P.K., S.M.A.; Design - P.K., S.M.A., M.G.F., R.J.; Supervision - P.K., S.M.A.; Materials - P.K., M.G.F.; Data Collection and/or Processing - P.K., R.J.; Analysis and/or Interpretation - S.M.A., M.G.F.; Literature Review - P.K., S.M.A.; Writing Manuscript - P.K., R.J.; Critical Review - P.K., S.M.A., M.G.F., R.J.

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