Novel insights in the prevention of perinatal transmission of hepatitis B

Konstantinos Tziomalos, Georgios Neokosmidis, Georgios Mavromatidis, Konstantinos Dinas

Konstantinos Tziomalos, Georgios Neokosmidis, First Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA Hospital, Thessaloniki 54636, Greece

Georgios Mavromatidis, Third Department of Obstetrics and Gynecology, Medical School, Aristotle University of Thessaloniki, Hippokration Hospital, Thessaloniki 54642, Greece

Konstantinos Dinas, Second Department of Obstetrics and Gynecology, Medical School, Aristotle University of Thessaloniki, Hippokration Hospital, Thessaloniki 54642, Greece

ORCID number: Konstantinos Tziomalos (0000-0002-3172-1594); Georgios Neokosmidis (0000-0003-1858-9098); Georgios Mavromatidis (0000-0003-3410-6826); Konstantinos Dinas (0000-0001-7144-2840).

Author contributions: Tziomalos K and Neokosmidis G drafted the editorial. Mavromatidis G and Dinas K critically revised the draft.

Conflict-of-interest statement: All authors declare no conflict of interest related to this publication.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Correspondence to: Konstantinos Tziomalos, MD, MSc, PhD, Assistant Professor, First Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA Hospital, 1 Stilponos Kyriakidi Street, Thessaloniki 54636, Greece. ktziomal@auth.gr
Telephone: +30-23-10994621
Fax: +30-23-10994773

Received: July 30, 2018
Peer-review started: July 30, 2018
First decision: August 8, 2018
Revised: August 14, 2018
Accepted: August 26, 2018
Article in press: August 27, 2018
Published online: November 27, 2018

Abstract

Perinatal transmission of hepatitis B virus (HBV) infection is major contributor to the growing burden of chronic hepatitis B worldwide. Administration of HBV immunoglobulin and HBV vaccination as soon after pregnancy as possible are the mainstay of prevention of perinatal transmission of HBV infection. In women with high viral loads, antiviral prophylaxis also appears to be useful. Lamivudine, telbivudine and tenofovir have been shown to be both safe and effective in this setting but tenofovir is the first-line option due to its low potential for resistance and more favorable safety profile.

Key words: Tenofovir; Perinatal transmission; Hepatitis B; Lamivudine; Telbivudine

© The Author(s) 2018. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Administration of hepatitis B virus (HBV) immunoglobulin and HBV vaccination as soon after pregnancy as possible are the mainstay of prevention of perinatal transmission of HBV infection. In women with high viral loads, antiviral prophylaxis with tenofovir also appears to be useful.

Tziomalos K, Neokosmidis G, Mavromatidis G, Dinas K. Novel insights in the prevention of perinatal transmission of hepatitis B. World J Hepatol 2018; 10(11): 795-798 Available from: URL:
INTRODUCTION

Perinatal transmission of hepatitis B virus (HBV) is a major healthcare problem, particularly in low-income countries with high prevalence of chronic hepatitis B (CHB)\(^1\). In regions where CHB is endemic, HBsAg(+) mothers transmit HBV in 70%-90% of their children if prophylaxis is not administered\(^2\). In addition, high HBV prevalence, poor compliance with medical care and barriers to health care among low-income population groups, especially in immigrants and Roma population, are associated with increased perinatal HBV transmission even in developed countries\(^2,3\). Women with high viral loads are at particularly increased risk to transmit hepatitis B to their offspring\(^4-7\). In many CHB endemic areas, perinatal transmission of hepatitis B is the major cause of transmission of hepatitis B\(^8,9\). Moreover, progression from HBV infection to CHB is substantially more frequent in the offspring of women with HBV DNA levels > 200000 IU/mL and/or > 6-7 log copies/mL\(^10-12\). On the other hand, a recent study reported that prompt administration of HBV immunoglobulin (i.e., within 4 h after birth) and/or an increase in the number of HBV vaccination doses (at birth and at 1, 2, 4 and 6 mo) resulted in very low rates of perinatal HBV transmission (2%) in HBsAg-positive women when HBV DNA levels > 200000 IU/mL\(^13\).

ROLE OF HBV IMMUNOGLOBULIN AND HBV VACCINATION

Administration of HBV immunoglobulin and HBV vaccination prevents most cases of perinatal HBV transmission\(^14\). Nevertheless, children born from women with high viral load are still at considerable risk for acquiring HBV despite the administration of HBV immunoglobulin and HBV vaccination [8%-18% when HBV deoxyribonucleic acid (DNA) levels are > 10\(^7\)-10\(^8\) copies/mL\(^6,12-14\)]. On the other hand, a recent study reported that prompt administration of HBV immunoglobulin (i.e., within 4 h after birth) and/or an increase in the number of HBV vaccination doses (at birth and at 1, 2, 4 and 6 mo) resulted in very low rates of perinatal HBV transmission (2%) in HBsAg-positive women with HBV DNA levels > 200000 IU/mL\(^15\).

ROLE OF NUCLEOSIDE ANALOGUES

Several studies also showed that nucleoside analogues combined with administration of HBV immunoglobulin and HBV vaccination are more effective in the prevention of perinatal HBV transmission than administration of HBV immunoglobulin and HBV vaccination alone\(^16\). In a meta-analysis of 5 small randomized controlled trials (RCTs, \(n = 444\) pregnant women), treatment with lamivudine combined with administration of HBV immunoglobulin and HBV vaccination reduced infant HBsAg seropositivity by 11.7% and infant HBV DNA positivity by 21.2% compared with administration of HBV immunoglobulin and HBV vaccination\(^17\). In a meta-analysis of 4 small RCTs (\(n = 293\) pregnant women), tenofovir also reduced infant HBsAg seropositivity by 15.8% and infant HBV DNA positivity by 16.2% compared to the control group\(^17\). Three early small nonrandomized studies (\(n = 307\) pregnant women) showed that tenofovir also reduces the risk for perinatal HBV transmission\(^18-20\). In a more recent RCT in HBeAg-positive mothers with viral load > 200000 IU/mL (\(n = 200\)), HBV transmission was observed in 5% of cases who received tenofovir in addition to HBV immunoglobulin/HBV vaccination compared with 18% in mothers treated with HBV immunoglobulin/HBV vaccination alone\(^14\). In contrast, in a larger RCT (\(n = 331\)), tenofovir combined with HBV immunoglobulin/HBV vaccination did not reduce the risk of HBV transmission compared with HBV immunoglobulin/HBV vaccination alone\(^15\). However, rates of HBV transmission in the latter group were very low (2%) and it is possible that the study was not powered to show superiority of tenofovir\(^15\).

Very few studies compared the efficacy of different nucleoside analogues in the prevention of perinatal HBV transmission. In two non-randomized studies (\(n = 690\) pregnant women), lamivudine was equally effective with tenofovir\(^21-22\) and in another non-randomized study (\(n = 120\) pregnant women), lamivudine was similarly effective with tenofovir\(^18\). Lamivudine, telbivudine and tenofovir also appear to be safe during pregnancy and do not increase the risk of congenital malformation, prematurity or maternal complications\(^17,23\). However, it should be emphasized that tenofovir and telbivudine are both Food and Drug Administration (FDA) pregnancy category B drugs (i.e., no risk in animal studies, unknown in humans) whereas lamivudine is FDA pregnancy category C drug (i.e., teratogenic in animal studies, unknown in humans)\(^24\). It has also been shown that in the United States, a country with very low prevalence of CHB, combining a nucleoside analogue with HBV immunoglobulin/HBV vaccination is more cost-effective than HBV immunoglobulin/HBV vaccination alone\(^25\). Nevertheless, it should be emphasized that none of these agents are licensed for use during pregnancy.

Current guidelines recommend screening of all pregnant women for CHB during the first trimester of pregnancy\(^24,26,27\). In all pregnant women with HBV DNA levels > 200000 IU/mL and/or > 6-7 log copies/mL or HBsAg levels > 4 log copies/mL, antiviral prophylaxis with tenofovir should start at week 24-32 of gestation and continue for up to 4-12 wk after delivery\(^24,26,27\). Tenofovir is preferred over lamivudine and telbivudine because of lower resistance rates and because it is a FDA pregnancy category B drug\(^24,26,27\).

ROLE OF CAESAREAN SECTION

The role of caesarean section in the prevention of perinatal transmission of HBV infection is unclear. In a recent meta-analysis of 10 studies (\(n = 5091\) new-
borns), caesarean section reduced the incidence HBV transmission by 38% compared with vaginal delivery (95%CI: 0.40–0.98; P = 0.04) [28]. However, the benefit of caesarean section was smaller in studies where hepatitis B immunoglobulin was administered to all women [28]. Moreover, caesarean section did not reduce the risk of vertical HBV transmission in HBsAg(+) women [28]. Accordingly, current guidelines do not recommend caesarean section for the prevention of perinatal transmission of HBV infection due to insufficient data [28].

BREASTFEEDING IN HBsAg(+) WOMEN

Regarding breastfeeding, current guidelines state that it is not contraindicated in HBsAg(+) women who are not receiving nucleoside analogues, since breast milk contains the lowest concentrations of HBV among body fluids and breast feeding does not increase the risk of HBV transmission in women who receive HBV immunoglobulin and HBV vaccination [24,26,27,29]. Moreover, breastfeeding is also not prohibited in women who are receiving prophylaxis with tenofovir, since this agent is excreted in very small amounts in breast milk [24,26,27,30,31].

CONCLUSION

Perinatal transmission of HBV infection is major contributor to the growing burden of CHB worldwide. Administration of HBV immunoglobulin and HBV vaccination as soon after pregnancy as possible are the mainstay of prevention of perinatal transmission of HBV infection. In women with high viral loads, antiviral prophylaxis with tenofovir also appears to be useful. Strategies to improve the awareness of this major healthcare problem are also needed to curb the rising incidence of CHB infection.

REFERENCES

1. Lee C, Gong Y, Brok J, Boxall EH, Gluud C. Effect of hepatitis B immunisation in newborn infants of mothers positive for hepatitis B surface antigen: systematic review and meta-analysis. BMJ 2006; 332: 328–336 [PMID: 16443611 DOI: 10.1136/bmj.38719.435833.7C]

2. Papaevangelou V, Hadjichristodoulou C, Cassimos D, Theodori­ dou M. Adherence to the screening program for HBV infection in pregnant women delivering in Greece. BMC Infect Dis 2006; 6: 84 [PMID: 16681862 DOI: 10.1186/1471-2334-6-84]

3. Drazilova S, Janicko M, Kristian P, Schreter I, Halanov M, Urbancikova I, Madarasova­ Geckova A, Marekova M, Pella D, Jarcuska P; HepaMeta Team. Prevalence and Risk Factors for Hepatitis B immunisation in newborn infants of mothers positive for hepatitis B surface antigen – systematic review and meta­analy­sis. J Hepatol 2011; 55: 999–603 [PMID: 21924740 DOI: 10.1016/j.jhep.2011.03.008]

4. Tassopoulos NC, Papaevangelou GJ, Sjogren MH, Roumeliotou­ Karayannis A, Gerin JL, Purcell RH. Natural history of acute hepatitis B surface antigen­positive hepatitis in Greek adults. Gastroenterology 1987; 92: 1418–1423 [PMID: 3569758 DOI: 10.1016/0016­5065(87)90644­7]

5. Pan CQ, Duan Z, Dai E, Zeng S, Han G, Yang W, Zang H, Zou H, Zhu B, Zhao W, Jiang H; China Study Group for the Mother­to­Child Transmission of Hepatitis B. Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load. N Engl J Med 2016; 374: 2324–2334 [PMID: 27300512 DOI: 10.1056/NEJMoa1506860]

6. Jurdain G, Ngo-Giang-Huong N, Harrison L, Decker L, Khumadaw L, Tierney C, Salvadori N, Cressey TR, Sirirungsi W, Morgan S, Pellan S, Sablon­pour A, A good practice to reduce the risk of perinatal transmission of hepatitis B virus infection. J Hepatol 2018; 69: 2324–2334 [PMID: 27300512 DOI: 10.1056/NEJMoa1506860]

7. Zou H, Chen Y, Duan Z, Zhang H, Pan C. Virologic factors associated with failure to passive-active immunoprophylaxis in infants born to HBsAg­positive mothers. J Viral Hepat 2012; 19: e18–e25 [PMID: 22239517 DOI: 10.1111/j.1365­2893.2011.01492.x]

8. Beasley RP, Hwang LY, Lin CC, Leu ML, Stevens CE, Szmuszn W, Chen KP. Incidence of hepatitis B virus infections in preschool children in Taiwan. J Infect Dis 1982; 146: 198–204 [PMID: 7108271 DOI: 10.1093/infdis/146.2.198]

9. After MJ, Hadler SC, Margolis HS, Alexander WJ, Hu PY, Judson FN, Mares A, Miller JK, Moyer LA. The changing epidemiology of hepatitis B in the United States. Need for alternative vaccination strategies. JAMA 1999; 282: 1218–1222 [PMID: 2304237 DOI: 10.1001/jama.1999.03440090020520]

10. McMahon BJ, Alward WL, Hall DB, Heyward WL, Bender TR, Francis DP, Maynard JE. Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. J Infect Dis 1985; 151: 599–603 [PMID: 3973412 DOI: 10.1093/infdis/151.4.599]

11. de Canho R, Grosheide PM, Mazel JA, Heijtink RA, Hop WC, Francoo L, Hazes S, Hop WC, Johannes TG, Verberken C, Schalm SW. Ten­year neonatal hepatitis B vaccination program, The Netherlands, 1982–1992: protective efficacy and long­term immunogenicity. Vaccine 1997; 15: 1624–1630 [PMID: 9364693 DOI: 10.1016/S0264­410X(97)00080­7]

12. Pan CQ, Duan Z, Dai E, Zeng S, Han G, Yang W, Zang H, Zou H, Zhu B, Zhao W, Jiang H; China Study Group for the Mother­to­Child Transmission of Hepatitis B. Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load. N Engl J Med 2016; 374: 2324–2334 [PMID: 27300512 DOI: 10.1056/NEJMoa1506860]

13. Jurdain G, Ngo-Giang-Huong N, Harrison L, Decker L, Khumadaw L, Tierney C, Salvadori N, Cressey TR, Sirirungsi W, Morgan S, Pellan S, Sablon­pour A, A good practice to reduce the risk of perinatal transmission of hepatitis B virus infection. J Hepatol 2018; 69: 2324–2334 [PMID: 27300512 DOI: 10.1056/NEJMoa1506860]

14. Tassopoulos NC, Papaevangelou GJ, Sjogren MH, Roumeliotou­ Karayannis A, Gerin JL, Purcell RH. Natural history of acute hepatitis B surface antigen­positive hepatitis in Greek adults. Gastroenterology 1987; 92: 1418–1423 [PMID: 3569758 DOI: 10.1016/0016­5065(87)90644­7]

15. Pan CQ, Duan Z, Dai E, Zeng S, Han G, Yang W, Zang H, Zou H, Zhu B, Zhao W, Jiang H; China Study Group for the Mother­to­Child Transmission of Hepatitis B. Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load. N Engl J Med 2016; 374: 2324–2334 [PMID: 27300512 DOI: 10.1056/NEJMoa1506860]

16. Jurdain G, Ngo-Giang-Huong N, Harrison L, Decker L, Khumadaw L, Tierney C, Salvadori N, Cressey TR, Sirirungsi W, Morgan S, Pellan S, Sablon­pour A, A good practice to reduce the risk of perinatal transmission of hepatitis B virus infection. J Hepatol 2018; 69: 2324–2334 [PMID: 27300512 DOI: 10.1056/NEJMoa1506860]

17. Cholongitas E, Tiwari MD, Marinos G, Li XM, Shi MF, Yang YB, Shi ZJ, Hou HY, Shen HM, Teng BQ. Effect of hepatitis B immunoglobulin on interruption of HBV intrauterine infection. World J Gastroenterol 2004; 10: 3215–3217 [PMID: 15457570 DOI: 10.3748/wjg.v10.i21.3215]

18. Beasley RP, Hwang LY, Lin CC, Leu ML, Stevens CE, Szmuszn W, Chen KP. Incidence of hepatitis B virus infections in preschool children in Taiwan. J Infect Dis 1982; 146: 198–204 [PMID: 7108271 DOI: 10.1093/infdis/146.2.198]
Celen MK, Mert D, Ay M, Dal T, Kaya S, Yildirim N, Gulsun S, Barcin T, Kalkanli S, Dal MS, Ayaz C. Efficacy and safety of tenofovir disoproxil fumarate in pregnancy for the prevention of vertical transmission of HBV infection. *World J Gastroenterol* 2013; 19: 9377-9382 [PMID: 24409065 DOI: 10.3748/wjg.v19.i48.9377]

Chen HL, Lee CN, Chang CH, Ni YH, Shyu MK, Chen SM, Hu JJ, Lin HH, Zhao LI, Mu SC, Lai MW, Lee CL, Lin HM, Tsai MS, Hsu JJ, Chan KS, Chang MH; Taiwan Study Group for the Prevention of Mother-to-Infant Transmission of HBV (PreMIT Study); Taiwan Study Group for the Prevention of Mother-to-Infant Transmission of HBV PreMIT Study. Efficacy of maternal tenofovir disoproxil fumarate in interrupting mother-to-infant transmission of hepatitis B virus. *Hepatology* 2015; 62: 375-386 [PMID: 25851052 DOI: 10.1002/hep.27837]

Yu MM, Jiang Q, Ji Y, Wu KH, Ju LL, Tang X, Yang YF. Comparison of telbivudine versus lamivudine in interrupting perinatal transmission of hepatitis B virus. *J Clin Virol* 2014; 61: 55-60 [PMID: 24994007 DOI: 10.1016/j.jcv.2014.06.005]

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* 2014; 60: 468-476 [PMID: 25187919 DOI: 10.1002/hep.27034]

Brown RS Jr, Verna EC, Pereira MR, Tilson HH, Aguilar C, Lea CS, Buti M, Fagan EA. Hepatitis B virus and human immunodeficiency virus drugs in pregnancy: findings from the Antiretroviral Pregnancy Registry. *J Hepatol* 2012; 57: 953-959 [PMID: 22766470 DOI: 10.1016/j.jhep.2012.06.031]

Sarin SK, Kumar M, Lai GK, Abbas Z, Chan HL, Chen CJ, Chen DS, Chen HL, Chen PJ, Chien RN, Dokmei AK, Gane E, Hou JL, Jafri W, Jia J, Kim JH, Lai CL, Lee HC, Lin SG, Liu CJ, Locarnini S, Al Mahtab M, Mohamed R, Omata M, Park J, Piratvisuth T, Sharma BC, Sollano J, Wang FS, Wei L, Yuen MF, Zheng SS, Kao JH. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int* 2016; 10: 1-98 [PMID: 26563120 DOI: 10.1007/s12072-015-9675-4]

Fan L, Owusu-Edusei K Jr, Schillie SF, Murphy TV. Cost-effectiveness of active-passive prophylaxis and antiviral prophylaxis during pregnancy to prevent perinatal hepatitis B virus infection. *Hepatology* 2016; 63: 1471-1480 [PMID: 26509655 DOI: 10.1002/hep.28310]

Terraulet NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS Jr, Bzowej NH, Wong JB. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018; 67: 1560-1599 [PMID: 29405329 DOI: 10.1002/hep.29800]

European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; 67: 370-398 [PMID: 28427875 DOI: 10.1016/j.jhep.2017.03.021]

Chang MS, Gavini S, Andrade PC, McNabb-Baltar J. Cesarean section to prevent transmission of hepatitis B: a meta-analysis. *Can J Gastroenterol Hepatol* 2014; 28: 439-444 [PMID: 25229465 DOI: 10.1155/2014/350179]

Hill JB, Sheffield JS, Kim MJ, Alexander JM, Serely B, Wendel GD. Risk of hepatitis B transmission in breast-fed infants of chronic hepatitis B carriers. *Obstet Gynecol* 2002; 99: 1049-1052 [PMID: 12052598]

Benaboud S, Pruvost A, Coffie PA, Ekuévi DK, Urien S, Arrivé E, Blanche S, Théodoros F, Avit D, Dabis F, Tréluyer JM, Hirt D. Concentrations of tenofovir and emtricitabine in breast milk of HIV-1-infected women in Abidjan, Cote d’Ivoire, in the ANRS 12109 TEMAA Study, Step 2. *Antimicrob Agents Chemother* 2011; 55: 1315-1317 [PMID: 21713182 DOI: 10.1128/AAC.00514-10]

Mirochnick M, Taha T, Kreitchmann R, Nielsen-Saines K, Kamwenda N, Joao E, Pinto J, Santos B, Parsons T, Kearney B, Emel L, Herron C, Richardson P, Hudelson SE, Eshleman SH, George K, Fowler MG, Sato P, Mofenson L; HPTN 057 Protocol Team. Pharmacokinetics and safety of tenofovir in HIV-infected women during labor and their infants during the first week of life. *J Acquir Immune Defic Syndr* 2014; 65: 33-41 [PMID: 23979002 DOI: 10.1097/QAI.0b013e3182a921eb]
