Journal of Virus Eradication 8 (2022) 100076

Contents lists available at ScienceDirect

Journal of Virus Eradication

journal homepage: www.sciencedirect.com/journal/journal-of-virus-eradication

Original research

Efficacy of the hepatitis B vaccine alone in the prevention of hepatitis B perinatal transmission in infants born to hepatitis B e antigen-negative carrier mothers

Wenjun Zhang [a,1], Chenyu Xu [b,1], Yanjing Rui [c,1], Jie Chen [c], Tingmei Chen [b], Yimin Dai [c], Biyun Xu [d], Yali Hu [c,**], Junhao Chen [a,***], Yi-Hua Zhou [a,e,*]

[a] Department of Laboratory Medicine, Nanjing Drum Tower Hospital, Nanjing University Medical School, Nanjing, 210008, China
[b] Department of Obstetrics and Gynecology, Zhenjiang Fourth People's Hospital, Zhenjiang, China
[c] Department of Obstetrics and Gynecology, Nanjing Drum Tower Hospital, Nanjing University Medical School, Nanjing, China
[d] Department of Biomedical Statistics, Nanjing Drum Tower Hospital, Nanjing University Medical School, Nanjing, China
[e] Department of Infectious Diseases, Nanjing Drum Tower Hospital, Nanjing University Medical School, Nanjing, China

ARTICLE INFO

Keywords:
Hepatitis B virus
Mother-to-child transmission
Hepatitis B vaccine
Hepatitis B immunoglobulin
Hepatitis B e Antigen
Efficacy assessment

ABSTRACT

Background: Vertical mother-to-child transmission (MTCT) of the hepatitis B virus (HBV) remains an important issue. Timely administration of hepatitis B immunoglobulin (HBIG) and of the HBV vaccine is effective in preventing MTCT in infants born to HBV-infected mothers. However, HBIG is often not easily available in low-income countries or regions.

Methods: We compared in a retrospective cohort study the HBV vaccine efficacy alone and in combination with HBIG in preventing vertical MTCT in infants born to HBeAg-negative carrier mothers in Jiangsu province, China. Based on the administration of the HBV vaccine and HBIG shortly after birth, children were divided into two groups: Group 1, administration of the HBV vaccine alone, and Group 2, concurrent use of HBIG and of the HBV vaccine.

Results: A total of 620 infants born to HBeAg-negative carrier mothers were enrolled into this study. Group 1 included 195 children who had received the HBV vaccine alone after birth, and Group 2, 425 children who had received both HBIG and the HBV vaccine. Children were followed up to the age of 68 and 42 months, respectively. MTCT of HBV occurred in 0% (0/195) in Group 1 (HBV vaccine alone) and 0% (0/425) in Group 2 (HBV vaccine and HBIG) ($p = 1.00$).

Conclusion: In this retrospective cohort study, we found that HBV vaccination alone shortly after birth was effective in preventing MTCT of HBV in infants born to HBeAg-negative carrier mothers.

1. Introduction

Hepatitis B virus (HBV) infection is a global public health problem. It is estimated that around 250 million people are chronically infected with the virus.[1] Vertical mother-to-child transmission (MTCT) is the major route of HBV transmission in many parts of the world. Before the availability of HBV immunoprophylaxis, 10–30% of infants born to hepatitis B surface antigen (HBsAg)-positive carrier mothers with negative hepatitis B e antigen (HBeAg) and 70–90% of those born to positive HBeAg carrier mothers were chronically infected with HBV, respectively.[2–4]

Immunoprophylaxis with the HBV vaccine is most effective in preventing infection and has been adopted in national immunization programs of 190 countries or regions.[5] Because infants born to HBV-infected mothers are exposed to the virus at birth and during delivery, post-exposure immunoprophylaxis measures, or concurrent use

* Corresponding author. Departments of Laboratory Medicine and Infectious Diseases, Nanjing Drum Tower Hospital, Nanjing University Medical School, Nanjing, China.
** Corresponding author.
*** Corresponding author.
E-mail addresses: dtylhu@126.com (Y. Hu), nj_cjh@aliyun.com (J. Chen), zgr03summer@126.com (Y.-H. Zhou).
[1] These authors have contributed equally to this work.

https://doi.org/10.1016/j.jve.2022.100076
Received 28 February 2022; Accepted 16 June 2022
Available online 20 June 2022

of hepatitis B immunoglobulin (HBIG) and the HBV vaccine, are recommended by the World Health Organization (WHO) and many countries.[6] After implementation of this strategy, MTCT of HBV was reduced to 0-<0.1% and 5–10% in infants born to HBeAg-negative and HBeAg-positive carrier mothers, respectively.[7–12]

However, there are limitations to HBIG availability in many instances. Thus, its administration to infants born to HBV-infected mothers is not implemented in all countries or regions.[6] Previous studies have shown that immunization with the HBV vaccine alone in infants born to HBV-infected HBeAg-negative carrier mothers had the same protective efficacy as combining vaccine and HBIG[13,14] or that MTCT rates were not statistically different between children who had received the vaccine alone and those who had received both HBIG and the vaccine.[15] The present retrospective cohort study reviews the use of the HBV vaccine alone and in combination with HBIG in the prevention of MTCT of HBV in infants born to HBV carrier HBeAg-negative mothers in Jiangsu province, China.

2. Methods

2.1. Study subjects

China has implemented a nationwide policy of universal HBV vaccination in all infants since 2002 with a free three dose HBV vaccine at 0, 1, and 6 months. In addition, HBIG has been recommended for newborns of HBsAg-positive mothers. However, the actual administration of HBIG had been suboptimal before the implementation of a nationwide program to administer free HBIG (100 IU) in all newborns of HBsAg-positive mothers which started from July 2011.[16] Thus, a considerable proportion of infants of HBsAg-positive mothers born before July 2011 did not receive HBIG at birth.

The present study is a retrospective analysis of the outcome of HBV infection in 620 children born between August 2002 and June 2011 from a Jiangsu provincial population-based project on birth defects (205 children), Nanjing Drum Tower Hospital (252 children) in Nanjing city, and Zhenjiang Fourth People's Hospital (163 children) in Zhenjiang city, Jiangsu province (Fig. 1). Inclusion criteria for the mothers were: (1) HBsAg-positive and HBeAg-negative status during pregnancy; (2) an absence of anti-HBV agents use before pregnancy; (3) an absence of anti-HBV agents during pregnancy; and (4) an absence of co-infection with hepatitis A, C, D, and E, and the human immunodeficiency virus.

HBV infection in the pregnant women taking part into the project on birth defects was defined in 2009 by retrospectively testing for HBV serological markers in 6398 archived serum samples collected at 15–20 week gestation between August 2002 and July 2004 (Fig. 1a).[17] The use of HBIG and of the HBV vaccine in children of the mothers from the project on birth defects was checked using children's vaccination cards at follow-up visits conducted between October 2009 and March 2010, during which blood samples were collected after parents or guardians had given written signed consent.[16] The mothers' HBV infection status from the Nanjing Drum Tower Hospital and Zhenjiang Fourth People's Hospital was checked using case records during their in-patient stay for delivery; the administration of HBIG and of the HBV vaccine in children born in these two hospitals was checked using case records and children's vaccination cards at follow-up visits, which were conducted from September 2011 to November 2012 (Fig. 1b). Blood sampling was performed after signed consent taken from their parents or guardians.

Based on the administration of the HBV vaccine and of HBIG shortly after birth, children were divided into two groups: Group 1, administration of the HBV vaccine alone, and Group 2, concurrent use of HBIG and of the HBV vaccine. Demographic and clinical characteristics, including age, maternal HBV DNA level, alanine amino transferase (ALT) level, and immunization records, were retrospectively collected from hospitalization charts or measured on archived serum samples.

This study was approved by the Institutional Review Board of the Ethics Committee of each hospital (Nanjing Drum Tower Hospital,

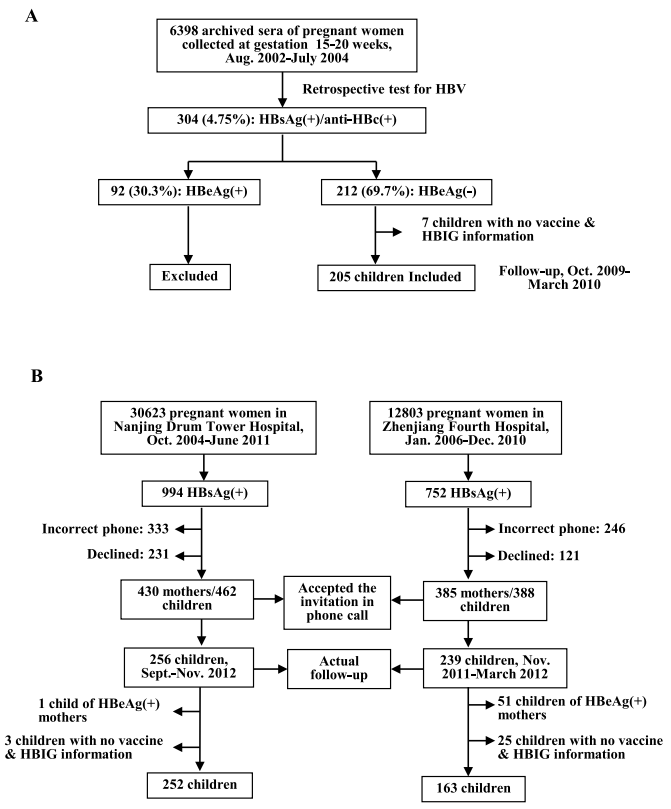

Fig. 1. Flow of subject enrollment. Abbreviations: HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; *anti*-HBs, antibody against HBsAg; HBeAg, hepatitis B e antigen; HBIG, hepatitis B immunoglobulin.

XK200709E; Zhenjiang Fourth People's Hospital, 2011016). Written informed consent was obtained from the children's parents/guardians.

2.2. Laboratory tests

Serum samples collected from the study children were tested by commercial ELISA kits for HBsAg, antibody to HBsAg (anti-HBs), HBeAg, antibody to HBeAg (anti-HBe), and antibody to HBV core antigen (anti-HBc) at Nanjing Drum Tower Hospital. HBsAg was tested with an ELISA kit (Huakang Biotech, Shenzhen, China) or microparticle enzyme immunoassay (Architect HBsAg, Abbott, North Chicago, USA). Anti-HBs and HBeAg were quantified with a microparticle enzyme immunoassay (AxSYM AUSAB, Abbott).

HBV DNA levels were measured in mothers during pregnancy by fluorescent quantitative polymerase chain reaction (PCR) with a lower detection limit of 100 IU/ml (Shenyou Biotech, Shanghai, China).

2.3. Definitions and statistical analysis

Children were classified with perinatally-acquired HBV infection if they tested positive for HBsAg at the age of 7 months or older. If negative for HBsAg and with anti-HBs titers ≥10 mIU/mL, they were defined as responders to HBV immunization. Anti-HBs levels of 10–99.99 mIU/mL, 100–999.99 mIU/mL and ≥1000 mIU/mL were defined as low, medium, and high levels, respectively.

Statistical analysis was performed using the IBM SPSS Statistics version 26 (SPSS Inc., Chicago, USA). Students *t*-test was used to compare statistical significance of differences in maternal age, HBV DNA level, and children age at follow-up between the two groups. Chi-square test was used to compare maternal ALT levels, distribution of children gender and anti-HBs positive rate between the two groups. Anti-HBs levels were expressed as median and range and compared using

Mann–Whitney U test. A p value < 0.05 was considered as statistically significant.

3. Results

3.1. Baseline characteristics of pregnant women and infants

Based on the administration of the HBV vaccine alone or in combination with HBIG shortly after birth, study children were divided into two groups: Group 1 with 195 children who had received the HBV vaccine alone, and Group 2 with 425 children who had received HBIG and the HBV vaccine. Demographic and clinical characteristics of these children and their mothers are shown in Fig. 2. Maternal age, ALT level and children's gender were comparable between the two groups with 95.3% in Group 1 and 99.1% in Group 2 having received the three-dose HBV vaccine ($p = 0.683$), respectively. The median age at follow-up in Group 1 (68 months) was higher than in Group 2 (42 months) ($p < 0.001$).

Fig. 3 shows that maternal HBV DNA was detectable in 79.0% of the mothers in Group 1 and in 75.3% of Group 2 ($P = 0.313$) (Fig. 3A). Median maternal HBV DNA levels (2.78 log IU/mL) in Group 1 were relatively higher than (2.62 log IU/mL) in Group 2 ($p = 0.025$) (Fig. 3B).

3.2. HBV infection in children

The HBV infection rate was 0.0% (0/195) for infants immunized with the HBV vaccine alone and 0.0% (0/425) for those who had received both the HBV vaccine and HBIG. No significant difference was found between the two groups ($p = 1.000$).

3.3. Anti-HBs levels in infants

As shown in Fig. 4A, overall rates of positive anti-HBs results in Group 1 and Group 2 children were 57.9% (113/195) and 68.9% (292/424), respectively ($p = 0.007$). Among these children, 66 in Group 1 and 348 in Group 2 were assessed for anti-HBs levels. Proportions of anti-HBs levels ≥1000, 100–999.99, 10–99.99, and <9.99 mIU/ml in Group 1 and Group 2 children are presented in Fig. 4B, with 9.1% (6/66), 13.6% (9/66), 42.4% (28/66), and 34.8% (23/66), respectively, in children immunized with the HBV vaccine alone, and 7.8% (27/348), 26.7% (93/348), 37.9% (132/348), and 27.6% (96/348), respectively, in children immunized with both HBIG and the HBV vaccine. The anti-HBs response of infants born to HBeAg-negative mothers was comparable in the two groups ($p = 0.186$).

4. Discussion

In the present retrospective study from a Jiangsu provincial population-based project on birth defects, we have found that among 620 children born to HBsAg-positive/HBeAg-negative mothers, none of the 195 children who had received the HBV vaccine alone after birth had been infected with HBV and none of the 425 children who had received a combination of HBIG and of the HBV vaccine were infected either. These results indicate that while the concurrent use of HBIG and of the HBV vaccine can almost completely stop MTCT of HBV in infants born to HBeAg-negative HBV carrier mothers, HBV vaccination alone was not associated with a difference in transmission in our study.

Maternal HBV DNA level is the main determining factor for MTCT of HBV.[18,19] Before the availability of HBIG and of the HBV vaccine, MTCT occurred in up to 70–90% of infants born to HBeAg-positive mothers, and in 5–30% of infants born to those who were HBeAg-negative.[2–4] The relatively low rate of MTCT in infants born to HBeAg-negative carrier mothers is mainly attributed to a lower viral exposure[20] with HBV DNA levels 10000–100000-fold lower than in HBeAg-positive mothers.[8,21–24] In the present study, none of the children born to HBeAg-negative carrier mothers were infected with HBV, irrespective of HBIG administration (Fig. 2), which indicates that HBV immunization alone in this population may have provided them with sufficient protection to prevent infection. An important parameter is the presence of low viral loads in the mothers with a median HBV DNA levels of 2.78 log IU/ml in Group 1 and of 2.62 log IU/ml in Group 2 (Fig. 3B).

Universal HBV immunization for infants had been introduced by the end of 2020 in the 190 Member States of the WHO, however, only 113 of them had introduced the HBV birth vaccine dose in neonates within 24 hours of birth, with a global overall coverage of 42%.[5] This low coverage is probably responsible for the HBV transmission in infants born to HBV-infected mothers or those cared by HBV-infected parents or guardians. The WHO has reported that the HBV prevalence in children younger than 5 years old was reduced in 2015 to 0.9% in the Western Pacific Region, where the coverage of the birth dose reached 84%, but

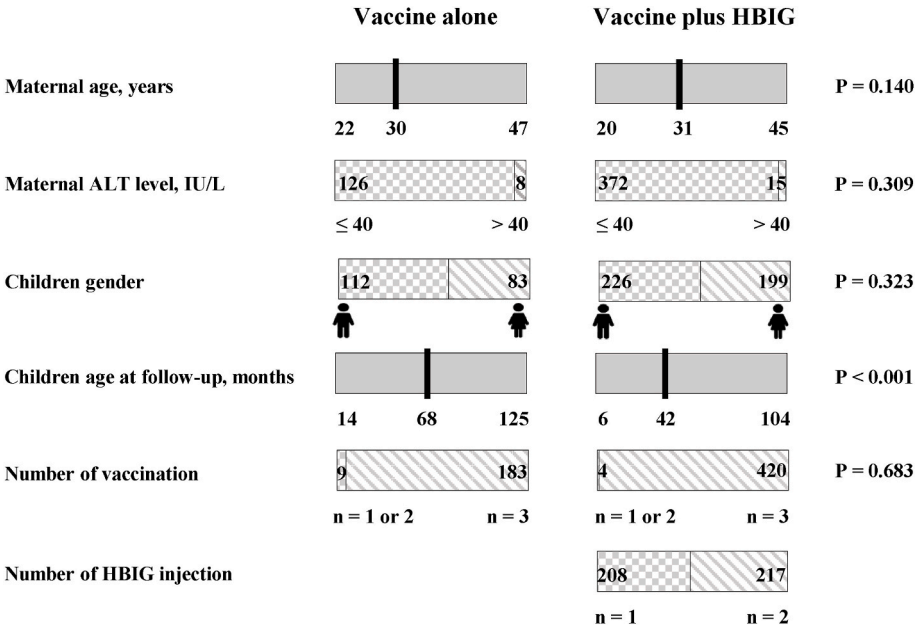

Fig. 2. The primary demographic and clinical characteristics of enrolled mothers and their neonates.

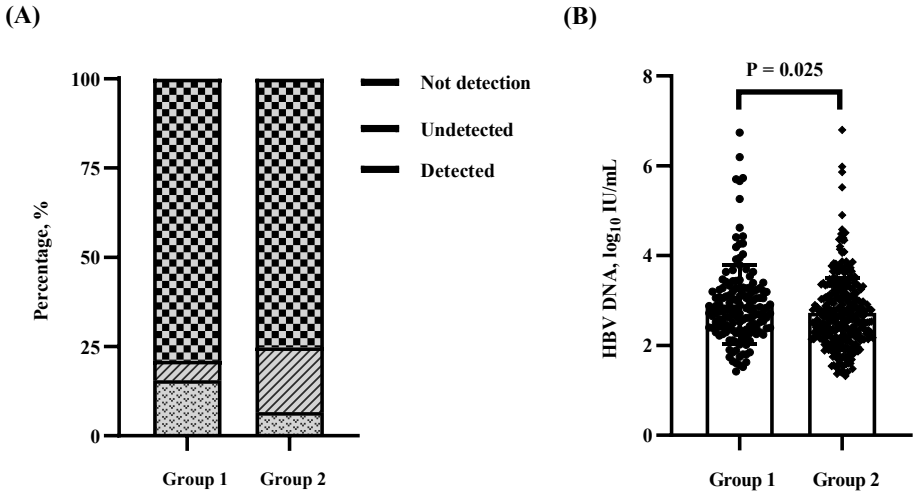

Fig. 3. **(A)** Detection rate and **(B)** distribution of HBV DNA levels among HBsAg-positive, HBeAg-negative pregnant women in the two groups.

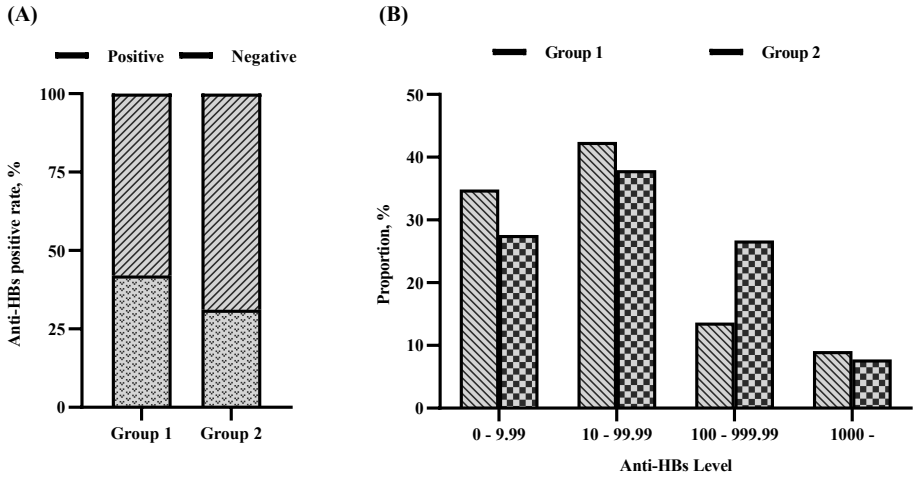

Fig. 4. **(A)** Anti-HBs positive rate and **(B)** distribution of anti-HBs levels among the infants with different prophylactic strategies in two groups.

prevalence was higher at 3.0% in the African Region, where the coverage of birth dose was only 6%.[1,6] In China, the coverage of a timely birth dose since 2012 has reached >95%, and the HBV prevalence in 2014 in children younger than 4 years old had declined to 0.3%, as compared to 10% before the availability of HBIG and HBV imminization.[25,26]

Several previous studies have demonstrated that the efficacy of HBV immunization on its own in infants of HBeAg-negative carrier mothers was almost equal to the concurrent use of HBIG and the HBV vaccine,[13,14] with an absence of perinatal infection in infants who had received the HBV vaccine alone.[27] Thus, some authors have considered that HBIG use in infants of HBeAg-negative carrier mothers had limited benefit in preventing MTCT.[13,15,28] However, larger studies of children immunized with the HBV vaccine alone have shown that there was still some residual degree of MTCT of HBV which occurred in children of HBeAg-negative carrier mothers,[15,29] whereas concurrent use of HBIG and the HBV vaccine almost completely prevented transmission.[7–12,30] As HBIG is safe and has no serious side-effects, the main concern remains its cost. However, because of the severe sequelae of chronic HBV acquired during infancy, it is cost-effective to use HBIG and the administration of the HBV vaccine alone is an option only when HBIG is not available. Therefore, every effort should be made to administer both HBIG and the HBV vaccine to infants of HBV-infected mothers, irrespective of maternal HBeAg status, to prevent MTCT of HBV.[18,31,32]

Ethics statement

This study was approved by the institutional review board of the ethics committee of each hospital (Nanjing Drum Tower Hospital, XK200709E; Zhenjiang Fourth People's Hospital, 2011016). Written informed consent was obtained from the parents/guardians, who signed the informed consent for children.

Author contributions

Wenjun Zhang, **Chenyu Xu**, **Yanjing Rui**, **Yali Hu**, **Junhao Chen**, and **Yi-Hua Zhou** designed the study. **Chenyu Xu**, **Yanjing Rui**, **Jie Chen**, **Tingmei Chen**, **Yimin Dai**, **Yali Hu**, and **Yi-Hua Zhou** followed up the participants. **Wenjun Zhang**, **Chenyu Xu**, **Yanjing Rui**, and **Jie Chen** performed laboratory testing. **Biyun Xu** performed the statistical analysis. **Wenjun Zhang**, **Chenyu Xu**, **Yanjing Rui** wrote the manuscript. **Yali Hu**, **Junhao Chen**, and **Yi-Hua Zhou** critically revised the manuscript. All authors interpreted the data, edited the manuscript, and approved the submitted version of manuscript.

Funding

This work was funded by the National Natural Science Foundation of China (81672002) and a grant from the Health Commission of Nanjing

City (ZKX20021), China.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1 World Health Organization. *Global Hepatitis Report 2017*. World Health Organization; 2017. https://apps.who.int/iris/handle/10665/255016.
2 Beasley RP, Trepo C, Stevens CE, et al. The e antigen and vertical transmission of hepatitis B surface antigen. *Am J Epidemiol*. 1977;105:94–98. https://doi.org/10.1093/oxfordjournals.aje.a112370.
3 Beasley RP, Hwang LY, Lee GC, et al. Prevention of perinatally transmitted hepatitis B virus infections with hepatitis B immune globulin and hepatitis B vaccine. *Lancet*. 1983;2:1099–1102. https://doi.org/10.1016/s0140-6736(83)90624-4.
4 Keane E, Funk AL, Shimakawa Y. Systematic review with meta-analysis: the risk of mother-to-child transmission of hepatitis B virus infection in sub-Saharan Africa. *Aliment Pharmacol Ther*. 2016;44:1005–1017. https://doi.org/10.1111/apt.13795.
5 WHO. *Immunization Coverage. Fact Sheet*; 15 July 2021. *Updated* http://www.who.int/mediacentre/factsheets/fs378/en/.
6 World Health Organization. *Prevention of Mother-To-Child Transmission of Hepatitis B Virus: Guidelines on Antiviral Prophylaxis in Pregnancy*. World Health Organization; 2020. https://apps.who.int/iris/handle/10665/333391.
7 Zhang L, Gui XE, Teter C, 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;32:6091–6097. https://doi.org/10.1016/j.vaccine.2014.08.078.
8 Wen WH, Huang CW, Chie WC, et al. Quantitative maternal hepatitis B surface antigen predicts maternally transmitted hepatitis B virus infection. *Hepatology*. 2016;64:1451–1461. https://doi.org/10.1002/hep.28589.
9 Cheung KW, Seto MTY, Kan ASY, et al. Immunoprophylaxis failure of infants born to hepatitis B carrier mothers following routine vaccination. *Clin Gastroenterol Hepatol*. 2018;16:144–145. https://doi.org/10.1016/j.cgh.2017.07.013.
10 Lu Y, Zhu FC, Liu JX, et al. The maternal viral threshold for antiviral prophylaxis of perinatal hepatitis B virus transmission in settings with limited resources: a large prospective cohort study in China. *Vaccine*. 2017;35:6627–6633. https://doi.org/10.1016/j.vaccine.2017.10.032.
11 Peng S, Wan Z, Liu T, et al. Incidence and risk factors of intrauterine transmission among pregnant women with chronic hepatitis B virus infection. *J Clin Gastroenterol*. 2019;53:51–57. https://doi.org/10.1097/MCG.0000000000001001.
12 Xu B, Xu C, Feng J, et al. Reduced mother-to-child transmission of hepatitis B after implementation of completely charge-free active-passive immunoprophylaxis: an observational cohort study. *Expert Rev Vaccines*. 2021;20:899–905. https://doi.org/10.1080/14760584.2021.1927723.
13 Yang YJ, Liu CC, Chen TJ, et al. Role of hepatitis B immunoglobulin in infants born to hepatitis B e antigen-negative carrier mothers in Taiwan. *Pediatr Infect Dis J*. 2003;22:584–588. https://doi.org/10.1097/01.inf.0000073123.93220.a8.
14 Lu Y, Liang XF, Wang FZ, et al. Hepatitis B vaccine alone may be enough for preventing hepatitis B virus transmission in neonates of HBsAg (+)/HBeAg (-) mothers. *Vaccine*. 2017;35:40–45. https://doi.org/10.1016/j.vaccine.2016.11.061.
15 Chen HL, Lin LH, Hu FC, et al. Effects of maternal screening and universal immunization to prevent mother-to-infant transmission of HBV. *Gastroenterology*. 2012;142:773–781 e2. https://doi.org/10.1053/j.gastro.2011.12.035.
16 Hu Y, Zhang S, Luo C, et al. Gaps in the prevention of perinatal transmission of hepatitis B virus between recommendations and routine practices in a highly endemic region: a provincial population-based study in China. *BMC Infect Dis*. 2012;12:221. https://doi.org/10.1186/1471-2334-12-221.
17 Zhang S, Li RT, Wang Y, et al. Seroprevalence of hepatitis B surface antigen among pregnant women in Jiangsu, China, 17 years after introduction of hepatitis B vaccine. *Int J Gynaecol Obstet*. 2010;109:194–197. https://doi.org/10.1016/j.ijgo.2010.01.002.
18 Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology*. 2018;67:1560–1599. https://doi.org/10.1002/hep.29800.
19 Zhou YH. Issues meriting further study in preventing mother-to-infant transmission of hepatitis B by antiviral therapy during pregnancy. *Matern Fetal Med*. 2019;1(1):43–47. https://doi.org/10.1097/FM9.0000000000000012.
20 Liu J, Xu B, Chen T, et al. Presence of hepatitis B virus markers in umbilical cord blood: exposure to or infection with the virus? *Dig Liver Dis*. 2019;51:864–869. https://doi.org/10.1016/j.dld.2018.11.003.
21 Liu J, Bi Y, Xu C, et al. Kinetic changes of viremia and viral antigens of hepatitis B virus during and after pregnancy. *Medicine (Baltim)*. 2015;94, e2001. https://doi.org/10.1097/MD.0000000000002001.
22 Xu C, Liu J, Liu L, et al. Comparison of hepatitis B viral loads and viral antigen levels in child-bearing age women with and without pregnancy. *BMC Pregnancy Childbirth*. 2018;18:292. https://doi.org/10.1186/s12884-018-1932-9.
23 Luo Y, Pan M, Ning M, et al. High mutation prevalence of precore and basal core promoter in pregnant women who underwent spontaneous HBeAg seroconversion within one year postpartum. *Dig Liver Dis*. 2020;52:199–204. https://doi.org/10.1016/j.dld.2019.06.021.
24 Boucheron P, Lu Y, Yoshida K, et al. Accuracy of HBeAg to identify pregnant women at risk of transmitting hepatitis B virus to their neonates: a systematic review and meta-analysis. *Lancet Infect Dis*. 2021;21:85–96. https://doi.org/10.1016/S1473-3099(20)30593-4.
25 Tang J, Luo YQ, Zhou YH. Elimination of hepatitis B virus infection in children: experience and challenge in China. *Chin Med J (Engl)*. 2021;134:2818–2824. https://doi.org/10.1097/CM9.0000000000001791.
26 Zhao H, Zhou X, Zhou YH. Hepatitis B vaccine development and implementation. *Hum Vaccines Immunother*. 2020;16:1533–1544. https://doi.org/10.1080/21645515.2020.1732166.
27 Milne A, West DJ, Chinh DV, et al. Field evaluation of the efficacy and immunogenicity of recombinant hepatitis B vaccine without HBIG in newborn Vietnamese infants. *J Med Virol*. 2002;67:327–333. https://doi.org/10.1002/jmv.10071.
28 Lee LY, Aw MM, Saw S, et al. Limited benefit of hepatitis B immunoglobulin prophylaxis in children of hepatitis B e antigen-negative mothers. *Singap Med J*. 2016;57:566–569. https://doi.org/10.11622/smedj.2015194.
29 Wang F, Zheng H, Zhang G, et al. Effectiveness of prevention of mother-to-child transmission practice in three provinces of Southern China. *Hum Vaccines Immunother*. 2015;11:2061–2067. https://doi.org/10.1080/21645515.2015.1023972.
30 Oon CJ, Lim GK, Ye Z, et al. Molecular epidemiology of hepatitis B virus vaccine variants in Singapore. *Vaccine*. 1995;13:699–702. https://doi.org/10.1016/0264-410x(94)00080-7.
31 Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the advisory committee on immunization practices. *MMWR Recomm Rep (Morb Mortal Wkly Rep)*. 2018;67:1–31. https://doi.org/10.15585/mmwr.rr6701a1.
32 Zhou YH, Hu Y, Liu X, et al. Maternal-Fetal Medicine Committee, Chinese Society of Obstetrics and Gynecology, et al. CSOG MFM Committee Guideline: management of hepatitis B during pregnancy and prevention of mother-to-child transmission of hepatitis B virus (2020). *Matern Fetal Med*. 2021;3(1):7–17. https://doi.org/10.1097/FM9.0000000000000087.