



2019 Chinese Clinical Practice Guidelines for the Prevention of Mother-to-child Transmission of Hepatitis B Virus

Jinfeng Liu^{#1,2}, Tianyan Chen^{#1,2}, Yaolong Chen^{#3,4}, Hong Ren^{*5}, Guiqiang Wang^{*6},
Wenhong Zhang^{*7}, Yingren Zhao^{*1,2} and Society of Infectious Diseases and Chinese Medical Association

¹The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China; ²Shaanxi Clinical Research Center of Infectious Diseases, Xi'an, Shaanxi, China; ³Evidence-Based Medicine Center, Basic Medical Sciences, Lanzhou University, Lanzhou, Gansu, China; ⁴WHO Collaborating Centre for Guideline Implementation and Knowledge Translation, Lanzhou, Gansu, China; ⁵Department of Infectious Diseases, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China; ⁶Hepatology Center, Department of Infectious Diseases, Peking University First Hospital, Beijing, China; ⁷Department of Infectious Diseases, Huashan Hospital Affiliated to Fudan University, Shanghai, China

Abstract

To develop the evidence-based guidelines for managing mother-to-child transmission of hepatitis B virus in China, a multidisciplinary guideline development group was established. Clinical questions were identified from two rounds of surveys on the concerns of first-line clinicians. We conducted a comprehensive search and review of the literature. A grading of recommendations' assessment, development, and evaluation system was adopted to rate the quality of evidence and the strength of recommendations. Recommendations were formulated based on the evidence, overall balance of benefits and harms (at individual and population levels), patient/health worker values and preferences, resources available, cost-effectiveness, and feasibility. Eventually, recommendations related to 13 main clinical concerns were developed, covering diagnostic criteria, treatment indications, antiviral therapy choice, timing to initiate and discontinue treatment, immunoprophylaxis strategy at birth, and how to deal with special situations, such as unintended pregnancy, assisted reproduction, and breastfeeding. The guidelines are intended to serve as guidance for clinicians

and patients, to optimize the management of majority of pregnant women who are positive for hepatitis B surface antigen. **Guideline registration:** International Practice Guide Registration Platform (IPGRP-2018CN040).

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Introduction

As a primary cause of liver cirrhosis and cancer, chronic hepatitis B (CHB), accounting for about 1 million deaths per year, remains a severe public health problem and presents a heavy disease burden and economic burden to society and families.¹ With an extensive hepatitis B vaccination program implemented, mother-to-child transmission (MTCT) has become the key obstacle to realizing the World Health Organization's goal of reducing the prevalence of hepatitis B surface antigen (HBsAg) among children aged 5, to 0.1%.² Furthermore, MTCT is responsible for familial clustering of hepatitis B virus (HBV) infection³ in which the risk of cirrhosis and hepatocellular carcinoma increase significantly and the age of onset of end-stage liver diseases was advanced dramatically.⁴ Elimination of MTCT is crucial to decreasing new HBV infections and to minimizing the burden of HBV-related diseases.

As the most principal strategy to prevent new HBV infections, the hepatitis vaccine has reduced the rate of MTCT by more than 80%.⁵ Whereas, among infants born to hepatitis B e antigen (HBeAg)-positive mothers, there are still 8% becoming CHB after vaccine immunoprophylaxis, and 4% after immunoprophylaxis of vaccine combined with human hepatitis B immunoglobulin (HBIG).⁵ Annually, there are almost 2 million new infections in children younger than 5 years. Antiviral intervention during pregnancy has been widely adopted to interrupt MTCT; nevertheless, there is still controversy about treatment indications, antiviral therapy choice, and the timing to initiate and discontinue the treatment, and so on.

Keywords: Hepatitis B virus; Mother-to-child transmission; Clinical practice guidelines; Prevention; GRADE.

Abbreviations: ADV, adefovir dipivoxil; AGREE II, Appraisal of Guidelines for Research and Evaluation; ALT, alanine aminotransferase; CHB, chronic hepatitis B; CK, creatine kinase; ETV, entecavir; GRADE, grading of recommendations assessment, development, and evaluation; HBeAg, hepatitis B e antigen; HBIG, human hepatitis B immunoglobulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IFN, interferon; LAM, lamivudine; LdT, telbivudine; MTCT, mother-to-child transmission; PICOs, population, intervention, comparator, outcomes; RIGHT, Reporting Items for Practice Guidelines in Healthcare; TAF, tenofovir alafenamide; TDF, Tenofovir disoproxil fumarate; TFV, tenofovir; ULN, upper level of normal.

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*These authors contributed equally to this work.

Correspondence to: Yingren Zhao, Department of Infectious Diseases, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi 710061, China. Tel: +86-13509187086, Fax: +86-29-85324594, E-mail: zhaoyingren@mail.xjtu.edu.cn; Hong Ren, Department of Infectious Diseases, The Second Affiliated Hospital of Chongqing Medical University, Chongqing 400010, China. E-mail: renhong0531@vip.sina.com.cn; Guiqiang Wang, Hepatology Center, Department of Infectious Diseases, Peking University First Hospital, Beijing 100034, China. E-mail: john131212@sina.com; Wenhong Zhang, Department of Infectious Diseases, Huashan Hospital Affiliated to Fudan University, Shanghai 200040, China. E-mail: zhangwenhong@fudan.edu.cn

To further standardize the clinical recommendations for top concerns of first-line clinicians, a multidisciplinary guideline development group was established to comprehensively evaluate the evidence and overall balance of benefits and harms, while the guidelines do not cover the whole spectrum of prevention and treatment of MTCT. As with clinical practice guidelines, they provide general guidance to optimize management of the majority of pregnant patients infected with HBV, while clinical judgement considering a unique patient and reliability of clinical care should be considered. In addition, despite accumulated knowledge, areas of uncertainty still exist and therefore health care workers, patients, and public health authorities must continue to make choices based on evolving evidence. The guidelines have two versions: the Chinese language version published in the *Chinese Journal of Infectious Diseases* and the English language version, which is the current version.

Methods

The guidelines were launched by the Society of Infectious Diseases, Chinese Medical Association, supported by the Chinese Grading of Recommendations Assessment, Development and Evaluation (GRADE) Center in methodology, and developed according to the World Health Organization's Handbook for Guideline Development (2014).⁶ Appraisal of Guidelines for Research and Evaluation (known as AGREE II)⁷ and Reporting Items for Practice Guidelines in Healthcare (known as RIGHT) tool⁸ were also referred to. Three groups were established for developing the guidelines: steering committee, guidelines development panel, and guidelines secretary group. The steering committee consisted of 3 well-known experts in the field, with the following missions: 1) approve the use of population, intervention, comparator, outcomes (PICO), 2) supervise the literature search and systematic reviews, 3) check the grade of the evidence, 4) finalize the recommendations using a modified Delphi approach, and 5) approve the publication of the guidelines. A multidisciplinary guidelines development panel, including experts from across the country in infectious diseases, hepatology, obstetrics, pediatrics, and methodology, was established, and tasked with the following missions: 1) generate the scope of the guideline and draft the PICOs, 2) grade the quality of the evidence, 3) draft the preliminary recommendations, and 4) write and publish the draft guideline. The guidelines secretary group conducted systematic reviews and investigated patients' views and preferences. All members involved in guidelines development were required to disclose any potential conflicts of interest, which were reviewed by the chairs (Yingren Zhao and Yaolong Chen). No relevant conflict of interest was reported.

Before initiating the guidelines, we wrote the protocol and registered it in the International Practice Guidelines Registry Platform (<http://www.guidelines-registry.org/>, IPGRP-2018CN040). First, we collected questions reflecting clinicians' concerns through two rounds of questionnaire survey. Two hundred sixty-one copies of the questionnaire were collected from 98 facilities across mainland China, covering 26 provinces, municipalities, and autonomous regions. After deduplication and combination, 16 PICO questions were identified from among 68 clinical questions, based on importance grade. Published articles and conference abstracts were identified from PubMed, Embase, the Cochrane Library, and three Chinese literature databases (CNKI, WanFang, and CBM). The evidence synthesis group conducted systematic reviews and

other literature searches for each question. We finally conducted 11 new systematic reviews. The GRADE was used to evaluate and rate the quality of evidence body (Table 1).⁹ We then formulated recommendations and rated their strengths after comprehensive assessment of the quality of evidence, consideration of the overall balance of benefits and harms, patient/health worker values and preferences, cost-effectiveness, and feasibility. Finally, the guidelines development panel reached a consensus on each recommendation based on three rounds of Delphi survey and also reached a consensus on management algorithm for MTCT of HBV (Fig. 1). A flow chart describes the process of the guidelines development (Fig. 2).

Recommendations

The guidelines contain 24 recommendations on the top 13 concerns of clinicians, covering diagnostic criteria, monitoring and prevention during pregnancy, and breastfeeding, as well

Table 1. Grades of evidence and recommendations

Grade of evidence	Notes
High quality (A)	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality (B)	Further research is likely to have an important impact on our confidence in the estimate of effect and there is a possibility that it may change the estimate.
Low quality (C)	Further research is very likely to have an important impact on our confidence in the estimate of effect and may be substantially different from the estimate of the effect.
Very low quality (D)	The estimate of effect is very uncertain, and the true effect is likely to be substantially different from the estimate of effect.
Grade of recommendation	
Strong (1)	The Guideline Panel is confident that the desirable effects of an intervention outweigh its undesirable effects (strong recommendation for an intervention), or that the undesirable effects of an intervention outweigh its desirable effects (strong recommendation against an intervention).
Weak (2)	The desirable effects probably outweigh the undesirable effects (weak recommendation for an intervention) or undesirable effects probably outweigh the desirable effects (weak recommendation against an intervention) but less uncertain higher cost or resource consumption exists.

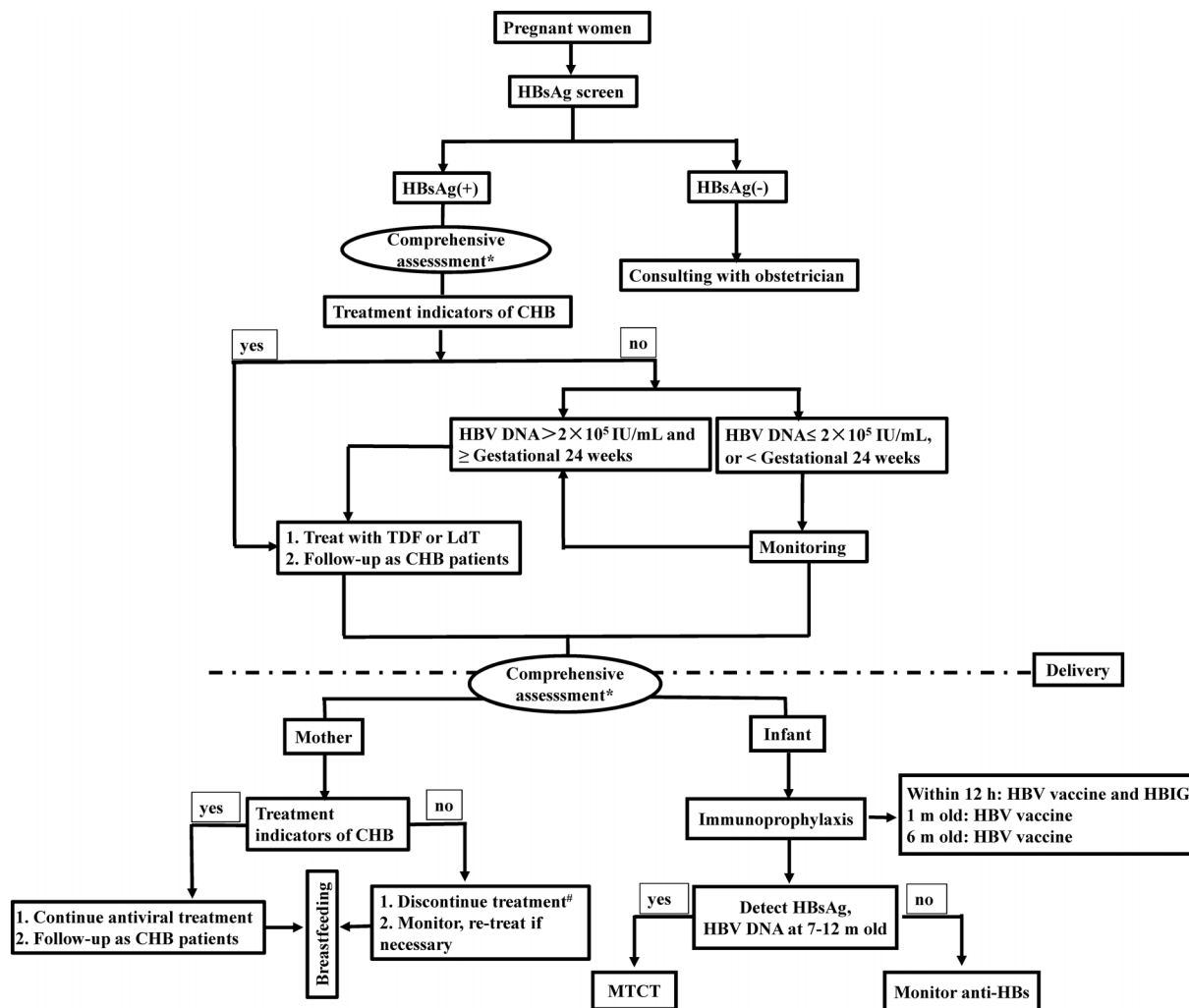


Fig. 1. Management algorithm for mother-to-child transmission of hepatitis B virus. *Comprehensive assessment: liver biochemical function, HBV DNA, imaging assessment; #Time to discontinue treatment: at delivery, postpartum 1 or 3 m old.

Abbreviations: CHB, chronic hepatitis B infection; HBIG, human hepatitis B immunoglobulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B Virus; m, months; MTCT, mother-to-child transmission; TDF, tenofovir disoproxil fumarate; LdT, telbivudine.

as immunoprophylaxis strategy at birth. All the recommendations are as follows.

Question 1: How to diagnose MTCT of HBV?
Recommendation: Infants with HBsAg and/or HBV DNA positive at 7-12 months-old are diagnosed as having CHB infection due to MTCT (1B).

Recommendation evidence

The previous reported rate of MTCT varied markedly, owing to inconsistency in specimens, timepoints of detection, and diagnostic criteria. Currently, HBsAg and/or HBV DNA positive at 7-12 months-old is deemed as having obtained CHB transmitted from mothers.^{10,11} Whereas, there is no systematic review to assess the criterion. A systematic review and network meta-analysis showed the rate of HBsAg and/or HBV DNA positive at birth in cord blood or venous blood was significantly higher than that at 6, 7, or 12 months-old,¹² which indicated the excessive positive rate at birth may be attributed to false positivity

caused by contamination of maternal blood or transient viremia due to placental abruption at birth.^{13,14} In addition, there was no significant difference among the positive rates at age of 6, 7 and 12 months.¹² Therefore, HBV serological markers and HBV DNA should be tested at 7-12 months-old, namely 1-6 months after three dosages of vaccination, to determine the immune results and infection status. Moreover, the infants over 12 months-old with HBsAg and/or HBV DNA positive at first visit are also supposed to acquire HBV infection by MTCT.

Question 2: What is the vaccination schedule for infants of HBsAg(+) mothers?

Recommendations:

2.1: The infants of HBsAg(+) mothers should receive hepatitis B vaccine and 100 IU HBIG within 12 h after birth, and the following two doses of vaccine at 1 and 6 months-old, respectively (1A).

2.2 For premature or low-birth weight infants, the combined immunoprophylaxis should be administered within 12 h after birth when the vital signs are stable or after the

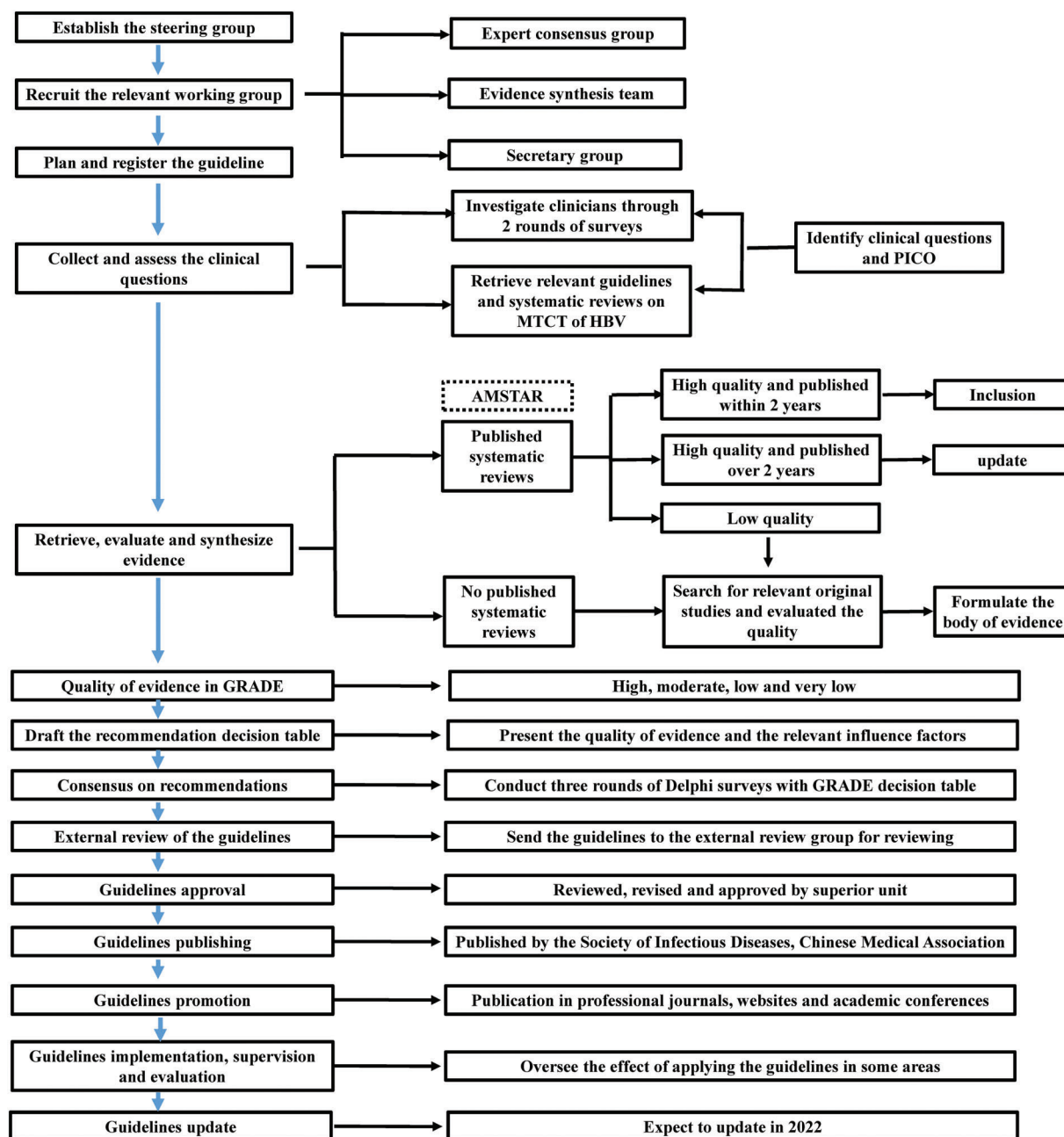


Fig. 2. Flowchart of the process of the guidelines development.

Abbreviations: GRADE, the Grading of Recommendations Assessment, Development and Evaluation; HBV, hepatitis B virus; MTCT, mother-to-child transmission; PICO, population, intervention, comparator, outcomes.

viral signs become stable. Three doses of full-course vaccine should be administered subsequently (1A).

Recommendation evidence

Combined immunoprophylaxis is the current standard immunoprophylaxis strategy for preventing MTCT in HBsAg(+) mothers. Several sets of guidelines¹⁵⁻¹⁹ recommend newborns of HBsAg(+) mothers receive hepatitis B vaccine

(10 µg recombinant yeast-derived hepatitis B vaccine or 20 µg recombinant Chinese hamster ovary cells hepatitis B vaccine) and HBIG, and vaccines are administered at 0, 1, and 6 months-old, respectively. For the premature or low-birth weight infants, one dose of vaccine is implemented as soon as possible within 12 h after birth (when the viral signs are stable) and another three doses of full-course vaccine are conducted after 1 month-old age is reached. For the very low-birth weight infants, those with severe birth defects, severe

asphyxia, or respiratory distress syndrome, should receive four doses of vaccine, administered after the vital signs become stable. By systematic review, we found 200 IU HBIG shows equivalent preventive effectiveness with 100 IU HBIG in infants born to CHB mothers (relative risk: 1.08, (0.64-1.82)) and HBeAg(+) mothers (relative risk: 0.84 (0.39-1.77)).²⁰ Considering cost-effectiveness, 100 IU HBIG is recommended to newborns of HBsAg (+) mothers.

Whether vaccine should be boosted in infants born to HBsAg(+) mothers is unclear. Systematic review also showed that the response to vaccine is similar between infants born to HBsAg(+) mothers and the general population.²¹ While the titer of anti-hepatitis B surface antibody should be regularly assessed, boost could be considered when the titer is less than 10 IU/mL, regarding the high-risk circumstances of infection.

Question 3: What is the threshold of HBV DNA for antiviral intervention during pregnancy?

Recommendations:

3.1 Antivirals should be recommended to pregnant women with HBV DNA $>2 \times 10^5$ IU/mL (1B).

3.2 Antiviral intervention could be decided after discussion with pregnant women with HBV DNA of 1×10^4 - 2×10^5 IU/mL (2C).

Recommendation evidence

Maternal high viremia is an independent risk factor for MTCT.²² The majority of guidelines from associations for the study of liver diseases, such as the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, the Asian Pacific Association for the Study of the Liver, and the National Institute for Health and Care Excellence, recommend antiviral intervention during pregnancy for preventing MTCT, whereas, the threshold of HBV DNA ranges from 2×10^5 IU/mL to 10^7 IU/mL.^{17,23-25} In addition, the recommendations are mainly based on clinical trials aiming to evaluating efficacy of antivirals^{11,26} or single retrospective cohort investigation.^{27,28}

A systematic review including 6027 patients from 18 studies indicated the rates of MTCT were 0, 0.88%, 1.15%, 4.81%, 10.04% and 18.80% in pregnant women with antenatal HBV DNA $<1 \times 10^4$ IU/mL, 1×10^4 IU/mL- 1×10^5 IU/mL, 1×10^5 IU/mL- 1×10^6 IU/mL, 1×10^6 IU/mL- 1×10^7 IU/mL, 1×10^7 IU/mL- 1×10^8 IU/mL, and $>1 \times 10^8$ IU/mL, respectively.⁵ The pooled rate of MTCT was as high as 10% in women with antenatal HBV DNA $\geq 1 \times 10^6$ IU/mL, which was remarkably higher than those with HBV DNA $<1 \times 10^6$ IU/mL. Antivirals should be recommended for these pregnant women. Pregnant women with HBV DNA of 1×10^4 IU/mL- 2×10^5 IU/mL still carry risk for transmitting the virus to their infants. Considering the high prevalence of HBsAg in China, antiviral intervention during pregnancy could be suggested in those with family history of HBV infection or history of MTCT. The benefit of antiviral treatment in terms of protecting newborns from HBV infection and controlling hepatitis activity in pregnant women with hepatitis should be explained before administration. At the same time, the patients should be notified of the side effects of antivirals, drug-resistant mutations, potential harms to the fetus, and hepatic flare after antivirals discontinuation, and so on.

Question 4: Which antivirals should be recommended for preventing MTCT?

Recommendations:

4.1. Tenofovir disoproxil fumarate (TDF) or telbivudine (LdT) is recommended for pregnant women with HBV DNA $>2 \times 10^5$ IU/mL (1B).

4.2 TDF is preferred in pregnant women with drug-resistance to lamivudine (LAM) or LdT (2C).

Recommendation evidence

TDF and LdT do not show reproductive toxicity in animal experiments.^{29,30} Plenty studies have manifested undifferentiated effectiveness of TDF and LdT in preventing MTCT.^{10,11,31} In addition, the frequency of adverse events in pregnant women receiving TDF or LdT, such as abnormal creatinine, postpartum hemorrhage, rate of cesarean section, birth defects, and preterm birth were comparable with general population.²⁶ A prospective cohort has demonstrated undifferentiated growth and development in infants born to LdT-treated pregnant women during 5 years' follow-up.³² For the pregnant women at high risk of MTCT, TDF or LdT should be administered to inhibit virus replication and reduce the transmission risk.

LAM and LdT present high potential of drug-resistance. Previous studies have confirmed the advantage of TDF over LAM and LdT as antiviral therapy.³³ Furthermore, the superiority of TDF has also been demonstrated in pregnant women with LAM or LdT-resistant mutants.³⁴ Hence, TDF could be suggested to pregnant women with drug-resistance to LAM or LdT.

As the first-line antiviral medicine for CHB patients, tenofovir alafenamide (TAF) has no influence on reproductive function in animal experiments. A study in human immunodeficiency virus-infected pregnant women assessed the safety of TAF but had small sample size.³⁵ The undergoing prospective, multicenter clinical trials will provide evidence for efficacy and safety of TAF in pregnant women with CHB.

Question 5: When should the antiviral be initiated to prevent MTCT during pregnancy?

Recommendation: The antiviral should be initiated at 24-28 weeks of gestation for preventing MTCT (2C).

Recommendation evidence

Head-to-head comparison of the efficacy and safety of different timepoints to initiate antiviral intervention is lacking. A Bayesian network meta-analysis and system review showed that the risk of MTCT decreased significantly in pregnant women accepting intervention before 28 weeks of gestation, as compared to those initiating after 28 weeks (relative risk: 0.019, (0.00034-0.19)).³⁶ Additionally, the efficacy and safety of antiviral therapy initiated from 24 weeks of gestation have been identified in cohort studies and case-control studies.^{10,11,31,37,38} Therefore, pregnant women with high HBV DNA levels ($>2 \times 10^5$ IU/mL) are recommended to initiate antiviral intervention at 24-28 weeks of gestation. For pregnant women with high viremia who are visiting the hospital after 28 weeks of gestation, antiviral intervention should be initiated immediately. For pregnant women with HBV DNA of 1×10^4 IU/mL- 2×10^5 IU/mL who agree to take antivirals, the intervention could be initiated no later than 28 weeks of gestation.

Question 6: How to manage unintended pregnancy during antiviral therapy?

Recommendation: For patients who become unintentionally pregnant during antiviral therapy, TDF or LdT treatment should be continued (2B); adefovir dipivoxil (ADV) or entecavir (ETV) should be switched to TDF (2C); the potential risks of interferon (IFN) should be fully informed, and the patient should switch to TDF if the patients and/or family members decide to carry on the pregnancy (2C).

Recommendation evidence

Data from the Antiretroviral Pregnancy Registry and well-controlled studies have revealed superior safety of TDF and LdT in pregnant women.^{10,11,31} Additionally, TDF shows great advantage in antiviral treatment because of superior resistance profile and more extensive safety data in pregnant women. A systematic review³⁹ showed the rate of birth defects as 0.66% in pregnant women exposed to nucleos(t)ide analogues, which are undifferentiated from the rate in Chinese population (5.6%)⁴⁰ and Metropolitan Atlanta Congenital Defects Program (2.8%).⁴¹ Therefore, childbearing women with unintended pregnancy during antiviral therapy should continue TDF or LdT.

The safety of ADV and ETV in pregnancy has not been elucidated clearly. A systematic review³⁹ including safety data from the Antiretroviral Pregnancy Registry showed the rate of birth defects in pregnant women exposed to ADV or ETV is comparable with that among the general population. Hence, women undergoing treatment of ADV or ETV could continue a pregnancy under doctors' guidance. However, regarding the risks of birth defects associated with high dose of ADV or ETV in animal experiments, switching to TDF is recommended.

We found low-quality evidence about the safety of IFN during pregnancy. Randomized controlled study of IFN administration during pregnancy is unlikely to be conducted, given the ethical concerns of such a trial. Guidelines suggest that IFN is contraindicated during pregnancy and contraception is recommended during IFN treatment,^{24,42,43} while how to deal with unintended pregnancy during IFN treatment causes substantial controversy between obstetricians and hepatologists. In a Rhesus monkey model, 90-180 times the recommended dosage of IFN led to increased rate of abortion. A series of cohort studies had displayed undifferentiated rates of adverse effects, including birth defects in pregnant women with essential thrombocythemia^{44,45} or multiple sclerosis^{46,47} following exposure to INF. In addition, in case reports, the infants born to HBV or hepatitis C virus/human immunodeficiency virus-infected mothers exposed to IFN during first trimester did not display abnormal rates of birth defects.⁴⁸⁻⁵⁰ The data from Bayer HealthCare's global pharmacovigilance database have not revealed an obvious increase of adverse effects in pregnant women exposed to IFN during the early trimester.^{47,51} With comprehensive assessment of toxicology, clinical reports, and views of obstetric experts, we suggest the risk of IFN should be fully informed to the pregnant women and their family members, and the TDF should be recommended instead of IFN if the family decides to continue the pregnancy.

Question 7: How to deal with HBsAg(+) pregnant women with hepatic flare?**Recommendations:**

7.1: For pregnant women with HBV DNA $\leq 2 \times 10^5$ IU/mL and ALT $< 2 \times$ the upper limit of normal (ULN), close monitoring should be conducted (2C).

7.2: If a hepatic flare is confirmed to be associated with immune activation, antiviral treatment and monitoring should be initiated as CHB patients (1C).

Recommendation evidence

We found low-quality evidence on management of hepatic flare during pregnancy. About 10% of pregnant women presents hepatic flare and the majority of those cases involve mild ALT elevation.^{52,53} For pregnant women with HBV DNA $\leq 2 \times 10^5$ IU/mL, mild ALT elevation ($< 2 \times$ ULN) and no cirrhosis, we suggest close monitoring without antiviral treatment, according to existing evidence.⁵²⁻⁵⁴ A proportion of CHB patients with mild ALT flare experience disease progression.²⁴ More evidence is required for treatment consideration in pregnant women with mild hepatitis flare.

For pregnant women with $2 \times \text{ULN} \leq \text{ALT} < 5 \times \text{ULN}$, close monitoring is recommended. If ALT continues fluctuating and hepatitis is attributed to immune activation, a treatment decision should be made.^{24,55} Pregnant women with advanced fibrosis or cirrhosis should initiate antiviral treatment immediately, and close monitoring is required throughout the pregnancy.

Question 8: Which indicators should be monitored during antiviral therapy for pregnancies?**Recommendations:**

8.1: For pregnant women taking antivirals to prevent MTCT, tests of liver biochemical function and HBV DNA should be conducted after 4 weeks (2C).

8.2: For those with hepatitis flares, more frequent monitoring and follow-up is recommended (2D). Renal function and serum phosphorus should be examined in patients receiving TDF, and creatine kinase (CK) should be measured in patients receiving LdT (2C).

Recommendation evidence

There is no consensus on monitoring timepoint and indicators examined in pregnant women undergoing antiviral treatment. A systematic review⁵⁶ showed a mean decrease of 3.16 log₁₀ IU/mL (95% confidence interval: 2.97-3.35) in HBV DNA after 4 weeks of antiviral treatment; therefore, HBV DNA level after 4 weeks of treatment can be tested to forecast the risk of transmission. HBV DNA levels should be tested again before delivery to further assess the risk.

There is potential influence on renal function and bone turnover⁵⁷ during long-term TDF treatment and risk of CK increase during LdT treatment.⁵⁸ In terms of the potential adverse effects, renal function and serum phosphorus should be examined in pregnant women with TDF treatment and CK during LdT treatment.

Question 9: Does HBV infection influence assisted reproduction?

Recommendation: Considering the comparable cleavage rate, embryo implantation rate, pregnancy rate, and abortion rate in infertile women with CHB, assisted reproduction could be conducted following the same

intervention and monitoring algorithm as in other CHB pregnant women (2C).

Recommendation evidence

The impact of HBV on assisted reproduction and pregnancy outcomes is uncertain. Studies about MTCT rate in infertile women are scarce. One case-control study⁵⁹ showed lower rate of fertilization, cleavage, high-quality embryos, and pregnancy in infertile women with HBV infection. In women with HBV DNA $\geq 5 \times 10^2$ IU/mL, few investigations have shown that ovarian reserve was lower and the rate of fertilization and high-quality embryos was decreased.^{60,61} Nevertheless, the systematic review we performed showed the rate of fertilization to be only a little lower, while there were not significant differences in the rate of cleavage, high-quality embryos, implantation, pregnancy, and abortion.⁶² In these circumstances, the infertile women with HBV infection could accept assisted reproduction. The intervention strategy should follow the recommendations for CHB pregnant women.

Question 10: Could amniocentesis be conducted in CHB pregnant women?

Recommendations:

10.1: Amniocentesis can increase the risk of MTCT in pregnant women with HBV DNA $\geq 1 \times 10^6$ IU/mL and can be conducted only if the potential benefit is considered definite after assessment by an obstetrician (2B).

10.2: Amniocentesis is feasible after weighing the benefits and harms in pregnant women with HBV DNA $< 1 \times 10^6$ IU/mL (2B).

Recommendation evidence

A previous systematic review⁶³ concluded that the risk of HBV transmission in amniocentesis was low in women with HBV DNA $< 1 \times 10^6$ IU/mL, whereas the risk increased significantly in HBeAg(+) mothers with HBV DNA $\geq 1 \times 10^6$ IU/mL (relative risk: 3.41-9.54). The 2018 updated American Association for the Study of Liver Diseases Guidelines recommend the risk of MTCT be considered when assessing the potential benefit of amniocentesis in women with high viremia.¹⁷ Therefore, for pregnant women with low viral load, amniocentesis could be conducted with signed written content; while for the women with high viremia ($\geq 1 \times 10^6$ IU/mL), the risk of MTCT should be assessed thoroughly and amniocentesis could be conducted for screening inherited and chromosomal diseases after consultation with an obstetrician.

Question 11: What is the influence of delivery mode on MTCT?

Recommendation: Cesarean section may reduce the risk of MTCT in pregnant women with antenatal HBV DNA $> 2 \times 10^5$ IU/mL without intervention during pregnancy, and could be considered when there is fetal distress, macrosomia, or overdue pregnancy (2C).

Recommendation evidence

With appropriate intervention and close monitoring, the risk of MTCT has decreased by a great degree, and the delivery mode does not affect MTCT. However, a portion of pregnant women do not undertake regular follow-up and appreciate intervention during pregnancy, especially in underdeveloped

regions, in this case, cesarean section could reduce the risk of MTCT (relative risk: 0.41, 95% confidence interval: 0.25~0.67, $p < 0.001$) in the pregnant women with antenatal HBV DNA $> 2 \times 10^5$ IU/mL.⁶³ This population could benefit from cesarean section for reducing MTCT. After comprehensive assessment of the evidence and standpoints expressed by obstetricians, we suggest that cesarean section may be considered when there is fetal distress, macrosomia, or overdue pregnancy. To prevent excessive cesarean section, obstetric indications should also be followed.

Question 12: When should the antiviral be discontinued after delivery?

Recommendations:

12.1: Pregnant women taking antivirals for preventing MTCT can discontinue antiviral treatment immediately after delivery, 4 weeks postpartum, or 12 weeks postpartum (2C), and should be monitored closely for hepatitis flare and rebound of HBV DNA (2C).

12.2: Pregnant women accepting antivirals owing to hepatic flare should be monitored and treated according to guidelines for CHB patients after delivery (2D).

Recommendation evidence

There are a series of changes to the immune system and body function during pregnancy. No consensus has been reached about the timepoint to discontinue antiviral treatment because of the insufficient evidence on this issue.^{17,24,64} Previous studies determined that about 20% of parturient women present ALT flare, regardless of antiviral treatment or not, and that there are two flare peaks, at 1 month postpartum and 3 months postpartum; the majority recover spontaneously.^{52,53,65,66} The net-meta analysis showed no difference in rate of hepatitis flare among mothers discontinuing antiviral treatment immediately after delivery, 4 weeks postpartum, and 12 weeks postpartum, and those without antiviral intervention during pregnancy.⁶⁷ In view of this, the pregnant women receiving antivirals for interrupting MTCT can discontinue treatment immediately after delivery, 4 weeks postpartum, or 12 weeks postpartum. HBV DNA could rebound after antiviral discontinuation; close monitoring should be conducted and re-antiviral treatment can be considered when meeting treatment indications for CHB therapy.^{24,55}

Previous studies of women who manifested ALT flare during pregnancy identified the occurrence as a risk factor for postpartum hepatic flare⁶⁶ and severe hepatitis has also been reported.⁶⁸ Therefore, it is suggested that pregnant women with active hepatitis should undergo monitoring and continue treatment after delivery, following guidelines for CHB patients.

Question 13: Could CHB mothers breastfeed?

Recommendations:

13.1: Breastfeeding is recommended after newborns accepting HBV vaccine and HBIG (2B).

13.2: The mother undergoing TDF treatment could give breastfeeding (2C).

Recommendation evidence

The research about breastfeeding in HBsAg(+) mothers is insufficient. One case-control study reported that the viral load in breast milk was related with maternal viral load⁶⁹ while the risk of transmission did not increase with high

maternal viremia.^{70,71} Further systematic review found that the risk of MTCT did not increase in infants accepting breastfeeding (relative risk: 0.73, $p=0.21$).⁷² Considering the significant benefit identified, breastfeeding is recommended to infants who undergo combined immunoprophylaxis.

The concentration of tenofovir (TFV) in breast milk and infants were 0.03% and 0.01% of recommended dose for infants from mothers with human immunodeficiency virus, respectively.^{73–75} In an investigation with small size of HBsAg (+) mothers undergoing TDF treatment, the TFV was undetectable in infants accepting breastfeeding. In addition, TFV cannot be absorbed via gastrointestinal tract. Hence, the mothers undergoing TDF treatment after delivery could give breastfeeding. Studies on infants accepting breastfeeding from LdT-treated mothers are scarce.

Conclusions

Clinical guidelines are derived from clinical concerns and are intended to direct practice. Major guidelines of prevention and treatment of CHB provide recommendations for pregnant women as a special population.^{17,23,24,55} The purpose of these guidelines is to provide scientific and specific guidance for the management of MTCT of HBV. Based on current clinical research outcomes, a preliminary exploration of the standardizations for managing MTCT has been established. Substantial relevant research evidence from China and other countries was fully retrieved and evaluated. Focusing on pregnant women with CHB, an expert panel from multiple disciplines proposed recommendations for the top 13 clinical concerns. Following accumulation of additional evidence and research findings, we plan to update the guidelines (at minimum) within 5 years of this publication (estimated 2022).

There are inevitably limitations to the process of guidelines' development that mainly reflect the low quality of the existing clinical studies and the small number of rigorously designed and implemented randomized controlled trials in this special population. For ethical issues, there is a lack of clinical trials on monitoring and treating CHB pregnant women with hepatitis flare; therefore, weak recommendations were proposed. In addition, scarce evidence exists on the rate of MTCT in infertile women with assisted reproduction, limiting the strength of recommendations. For infants born to CHB mothers, it is still essential to evaluate the necessity of booster vaccination. However, further scientific research will gradually address these shortcomings. Beyond that, as principal strategy, coverage of screening for HBsAg (+) in childbearing women and the vaccination program requires more efforts.

Development of these guidelines is a small step toward the goal of standardized diagnosis and optimized management of MTCT. It is hoped that these guidelines will facilitate clinical research, accumulate more high-quality evidence in the future, and ultimately promote the elimination of MTCT.

Members of the Guidelines Steering Committee

Taisheng Li, Guiqiang Wang, Kehu Yang

Members of the Guidelines Development Panel

Xuefan Bai, Hong Chen, Suhua Chen, Tianyan Chen, Xinyue Chen, Yaolong Chen, Mingliang Cheng, Xiaoguang Du, Xiangchun Ding, Shangrong Fan, Xuegong Fan, Zhiliang Gao, Yingli He, Peng Hu, Yanhong Huang, Yan Huang, Fanpu

Ji, Zhansheng Jia, Jianning Jiang, Peiru Jiang, Chengzhong Li, Chunfang Li, Fen Li, Jun Li, Ke Li, Xuelan Li, Yongguo Li, Zhengwen Liu, Qing Mao, Qinghua Meng, Qin Ning, Hong Ren, Hong Tang, Feng Wang, Jiuping Wang, Kai Wang, Jia Wei, Lai Wei, Yida Yang, Zujiang Yu, Li Zhang, Quan Zhang, Wenhong Zhang, Yuexin Zhang, Caiyan Zhao, Hong Zhao, Yingren Zhao

Members of the Guidelines Secretary Group

Yali Feng, Shan Fu, Jinfeng Liu, Naijuan Yao

Members of the Evidence Synthesis Team

Yanfang Ma, Juan Li, Xufei Luo, Changli Qian, Zhen Tian, Jianjian Wang, Yuchao Wu, Nan Yang, Jingyi Zhang, Qi Zhou

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Conflict of interest

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

Author contributions

Study concept and design (YRZ, GQW, WHZ, HR), drafting of the manuscript (JFL, TYC), critical revision of the manuscript for important intellectual content (YLC, WHZ, GQW, HR), administrative, study supervision (YRZ, GQW, WHZ, HR).

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