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Guideline

Chinese Clinical Practice Guidelines for the Prevention and Treatment of Mother-to-child Transmission of Hepatitis B Virus (Version 2024)

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Abstract

The *Chinese Clinical Practice Guidelines for the Prevention and Treatment of Mother-to-child Transmission of Hepatitis B Virus*, developed by the Chinese Society of Infectious Diseases of the Chinese Medical Association in 2019, serves as a valuable reference for standardizing the prevention of mother-to-child transmission in China. As new evidence continues to emerge, it is essential to update these guidelines regularly to optimize clinical practice and research. To this end, the Infectious Disease Physician Branch of the Chinese Medical Doctor Association and the Chinese Society of Infectious Diseases of the Chinese Medical Association, in collaboration with multidisciplinary experts, have updated the guidelines based on the latest domestic and international research advancements and clinical practices, providing up-to-date guidance for clinicians and maternal and child healthcare workers.

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Introduction

Mother-to-child transmission (MTCT) is the predominant route of hepatitis B virus (HBV) transmission in China, with a chronic infection rate of approximately 90% when the infection occurs during the perinatal or infant period.[1] Children infected with HBV subsequently become sources of horizontal transmission, while HBV-infected females can transmit the virus to the next generation through MTCT during childbirth; the latter is the major cause of familial clustering of HBV infection.[2] In families with a history of HBV infection, the risk of cirrhosis and hepatocellular carcinoma (HCC) is significantly higher. Among HBV-infected offspring, cirrhosis and HCC onset is about 10 years earlier,[2] and the risk of HCC is increased by 32.9-fold in those with a family history of HCC.[3] To combat this, the National Health Commission of the People's Republic of China has definitely proposed to eliminate HBV MTCT nationwide by 2025, as outlined in the *Action Plan for Eliminating Mother-to-child Transmission of Human Immunodeficiency Virus (HIV), Syphilis, and Hepatitis B Virus (2022–2025)*. Administering antiviral prophylaxis during pregnancy for women with high HBV viremia, combined with standard immunization protocols of hepatitis B vaccine and hepatitis B immunoglobulin (HBIG) for their infants, has been demonstrated to reduce the MTCT rate to 0.3%.[4] Additionally, a recent study has indicated that the interdisciplinary and cross-community clinical management system for the comprehensive prevention of HBV MTCT has further reduced the transmission rate to 0.23%,[5] providing crucial scientific support to the feasibility of eliminating MTCT.

In 2019, the Chinese Society of Infectious Diseases of the Chinese Medical Association and Chinese GRADE Center organized a multidisciplinary expert team to formulate the *Chinese Clinical Practice Guidelines for the Prevention and Treatment of Mother-to-child Transmission of Hepatitis B Virus* (version 2019, hereafter referred to as the "2019 Guidelines"),[6] which has since played a valuable role in standardizing the process of preventing HBV MTCT. Over the past five years, significant advancements in clinical research, both in

Table 1. GRADE assessment of the quality of evidence and strength of recommendations

Grade	Description
Quality of Evidence	
High (A)	Very confident that the observed effect is close to the true effect.
Moderate (B)	Moderately confident in the estimate of effect: the true effect is likely to be close to the observed effect, but there is a possibility that it is substantially different.
Low (C)	Limited confidence in the estimate of effect: the true effect may be substantially different from the observed effect.
Very Low (D)	Very little confidence in the estimate of effect: the true effect is likely to be substantially different from the observed effect.
Strength of Recommendations	
Strong (1)	Clearly indicates that the benefits of the intervention outweigh the risks or vice versa
Weak (2)	The benefits and risks are closely balanced or uncertain, regardless of the evidence quality

China and internationally, have been made in the prevention of HBV MTCT. From a clinical perspective, some of the recommendations in the 2019 Guidelines now require updating. This includes refining the management strategies for maternity care, particularly in the context of expanding the indications for antiviral treatment, and adjustment of antiviral medications in cases of unintended pregnancy. The 2019 Guidelines were also originally scheduled for revision within five years. Thus, to better support clinical practice and research in preventing HBV MTCT, the working group has updated the 2019 Guidelines based on a systematic review of the literature and evidence evaluation.

The newly updated *Chinese Clinical Practice Guidelines for the Prevention and Treatment of Mother-to-child Transmission of Hepatitis B Virus (version 2024)* (hereafter referred to as the "2024 Guidelines") aimed to guide professionals in infectious diseases, hepatology, obstetrics and gynecology, and maternal and child healthcare in managing chronic HBV-infected pregnant women and their infants. It is important to note that the recommendations in the 2024 Guidelines are not mandatory and do not cover every possible issue related to the prevention of HBV MTCT. Clinicians must consider the specific conditions and preferences of individual patients, utilize the best available clinical evidence, and make reasonable decisions based on professional expertise, clinical experience, and available medical resources. The 2024 Guidelines follow the Grades of Recommendations, Assessment, Development, and Evaluation system (hereinafter referred to as GRADE system) for grading the quality of evidence and strength of recommendations. The quality of evidence is categorized into four levels (A, B, C, and D), and recommendations are classified into two levels: strong (Level 1) and weak (Level 2) (Table 1).

Recommendations and Rationales

After evaluation by the Guideline Expert Panel and approval by the Steering Committee, the final version of the 2024 Guidelines includes 14 recommendations addressing 10 clinical issues. Figure 1 provides a concise flowchart summarizing these recommendations.

Clinical Question 1: What are the diagnostic criteria for chronic HBV infection resulting from MTCT?

Recommendation 1: For infants born to mothers with chronic HBV infection, the presence of hepatitis B surface antigen (HBsAg) and/or HBV DNA in venous blood at seven to twelve months of age indicates chronic HBV infection due to MTCT (1B). The presence of HBsAg and/or HBV DNA in neonatal venous blood should not be used as a diagnostic criterion for MTCT (1B).

Rationale: MTCT of HBV typically refers to the transmission of HBV from mother to child during the perinatal period, leading to chronic infection. Antibodies to hepatitis B core antigen can be detected in the venous blood of all neonates born to mothers with chronic HBV infection. Approximately 20% of these neonates have low levels of HBV DNA, HBsAg, and hepatitis B e antigen (HBeAg), with 90% clearing both HBsAg and HBV DNA by the age of seven months.[7,8] Therefore, routine testing for HBsAg and/or HBV DNA in neonates is not recommended.

Observational studies and a systematic review indicated significantly higher positivity rates for HBsAg and/or HBV DNA in newborns tested within the first 24 h of birth compared to infants at six, seven, or twelve months of age. The positivity rates are similar among infants tested at six, seven, or twelve months.[8,9] Hence, it is recommended to test for HBsAg and/or HBV DNA one to six months after completing the full hepatitis B vaccination series to confirm chronic HBV infection due to MTCT.

Clinical Question 2: What measures can be taken to prevent HBV MTCT?

Recommendation 2.1: Newborns of mothers with chronic HBV infection should receive their first dose of recombinant hepatitis B vaccine (10 μg yeast vaccine or 20 μg Chinese hamster ovary cell vaccine) as early as possible, within 12 h of birth, followed by the second and third doses at one month and six months of age, respectively (1A). For low-birth-weight or preterm infants, the first dose of the hepatitis B vaccine should be administered within 12 h of birth, as soon as vital signs are stable, followed by the standard "0-1-6 month" vaccination schedule (1A).

Rationale: Timely postnatal hepatitis B vaccination is the most critical measure for preventing HBV MTCT, reducing the transmission rate from 82.9% to 15.9% in HBeAg-positive mothers and from 10.3% to 2.3% in HBeAg-negative mothers.[4] The *Immunization Schedules and Instructions for Vaccines of the National Immunization Program*, issued by the National Health Commission of the People's Republic of China in 2021, provides detailed guidelines for the hepatitis B vaccination schedule for infants born to HBsAg-positive mothers. Newborns weighing less than 2,000 g should also receive the first dose of the hepatitis B vaccine as soon as possible after birth, with the subsequent two doses administered according to the "0-1-6 months" schedule. Furthermore, critically ill newborns such as those with extremely low birth weight

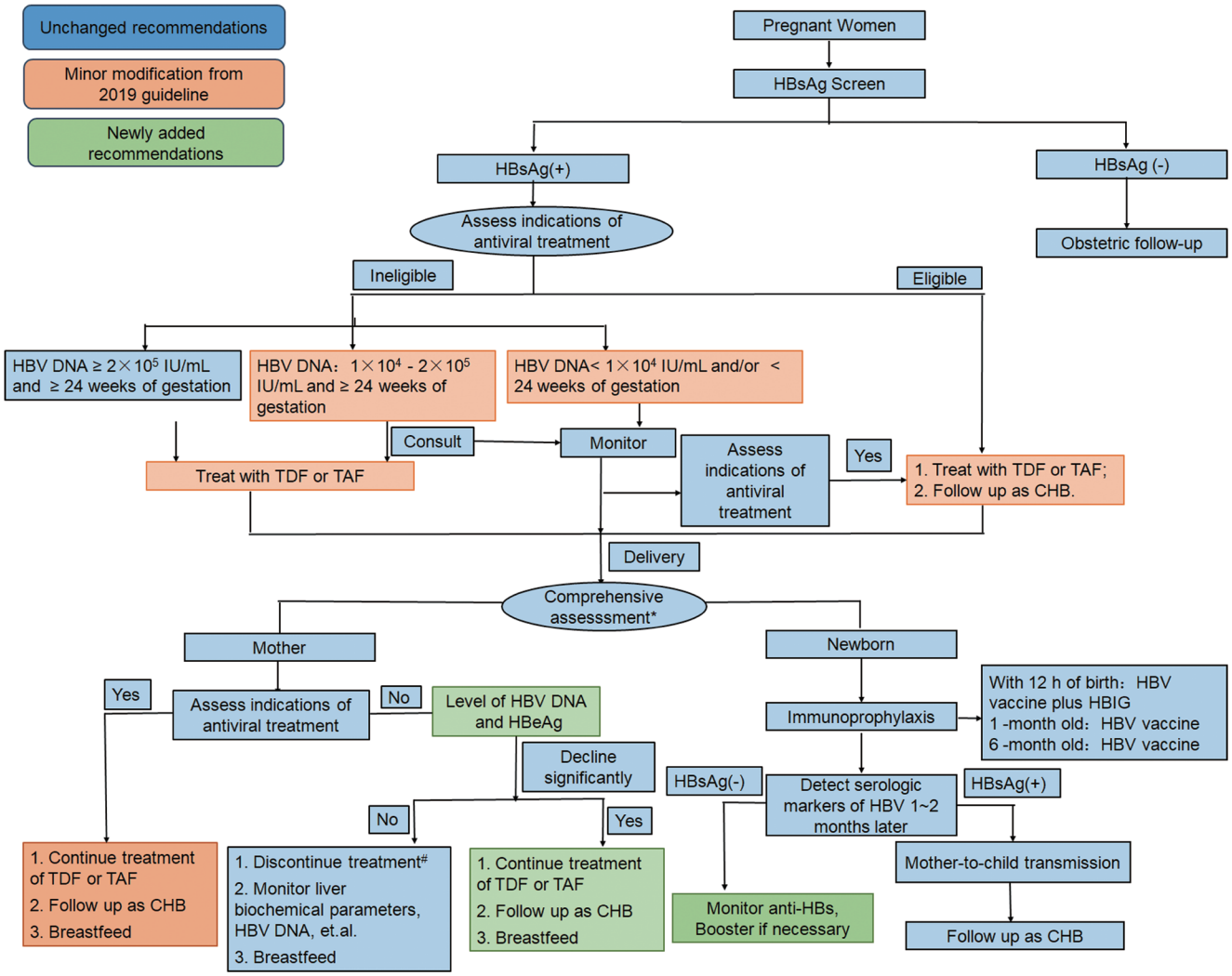

Fig. 1. Management algorithm for the prevention and treatment of mother-to-child transmission of hepatitis B virus. Comprehensive assesssment* includes liver biochemical parameters, serological markers of HBV, HBV DNA quantification, and abdominal ultrasound; Time to discontinuing treatment#: immediately postpartum to 3 months postpartum. HBV, Hepatitis B virus; HBsAg, Hepatitis B surface antigen; CHB, Chronic hepatitis B; TDF, Tenofovir disoproxil fumarate; TAF, Tenofovir alafenamide; HBeAg, Hepatitis B e antigen; HBIG, Hepatitis B immunoglobulin; Anti-HBs, Anti-hepatitis B surface antigen.

(<1,500 g), severe birth defects, severe asphyxia, or respiratory distress syndrome, should receive the first dose of the vaccine once their vital signs are stable.

Recommendation 2.2: Newborns of mothers with chronic HBV infection should receive a dose of 100 IU of HBIG at a site different from the hepatitis B vaccine as early as possible, within 12 h of birth (1A).

Rationale: HBIG, which contains anti-hepatitis B surface antigen (anti-HBs) as its active ingredient, serves as an effective form of passive prophylaxis for individuals who have been accidentally exposed to HBV. When administered promptly alongside the hepatitis B vaccine to neonates born to HBsAg-positive pregnant women, HBIG can significantly reduce the MTCT rate from 11.2% (95% confidence interval [CI]: 8.9–13.6%) to 8.1% (95% CI: 7.2–9.0%), and even further to 0.5% (95% CI: 0.1–1%) in infants born to HBeAg-negative mothers.[4] The National Immunization Program and various guidelines[10,11] recommend that neonates born to HBsAg-positive mothers receive both the hepatitis B vaccine and HBIG as early as possible, ideally within 12 h of birth.

Prospective cohort studies and systematic reviews showed equivalent preventive effectiveness between 100 IU and 200 IU HBIG in infants born to HBsAg-positive mothers, even in populations at high risk for transmission.[12,13] Therefore, a 100 IU dose of HBIG is recommended for neonates born to HBsAg-positive mothers.

The high cost of HBIG production and requirements of cold chain logistics have raised concerns about the cost-effectiveness of combined immunization with hepatitis B vaccine and HBIG for infants born to HBsAg-positive mothers, particularly among policymakers. One systematic review concluded that the hepatitis B vaccine alone is as effective as the combination of the vaccine and HBIG in preventing MTCT in infants born to HBeAg-negative mothers.[14] A prospective multicenter study evaluated the effectiveness of a strategy without HBIG. In pregnant women eligible for tenofovir disoproxil fumarate (TDF) treatment—namely, those who are HBeAg-positive or have alanine aminotransferase (ALT) levels above 40 IU/mL—the MTCT rate was found to be 1.0% (95% CI: 0.40–3.74%) in infants who received only the hepatitis B

vaccine. Additionally, none of the infants born to mothers who received TDF for more than four weeks before delivery were infected with HBV.[15] Given the evolving indications for antiviral treatment, the cost-effectiveness ratio for the combined use of the hepatitis B vaccine and HBIG in infants born to HBV-infected mothers warrants further assessment.

Recommendation 2.3: For pregnant women ineligible for antiviral treatment for chronic HBV infection, oral antiviral prophylaxis is recommended to prevent MTCT if their HBV DNA levels ≥ 2×10^5 IU/mL (1A). Pregnant women with HBV DNA levels ranging from 1×10^4 IU/mL to 2×10^5 IU/mL during mid to late pregnancy should engage in thorough discussions before deciding on oral antiviral prophylaxis (1B). In areas where HBV DNA quantification is unavailable, HBeAg positivity may be considered as a surrogate indicator for antiviral prophylaxis during pregnancy to prevent MTCT, although HBV DNA quantification is preferred when possible (2B).

Rationale: Maternal high viremia is an independent risk factor for MTCT. A systematic review by the World Health Organization (WHO) demonstrates that the MTCT rate exceeds 3.80% among pregnant women with HBV DNA levels ≥ 2×10^5 IU/mL, even when infants have received both the birth dose vaccine and HBIG.[16] Another systematic review with a larger sample size indicated that pregnant women with HBV DNA levels ranging from 1×10^4 to 2×10^5 IU/mL before delivery still face a 0.6% risk of MTCT (95% CI: 0.0–2.6%) despite their infants receiving combined immunization. This risk exceeds the rate of 0.23% recently reported in a domestic study.[5] Based on these findings, the 2024 Guidelines recommend that pregnant women with HBV DNA levels ≥ 2×10^5 IU/mL receive antiviral prophylaxis to prevent MTCT. For those with HBV DNA levels ranging from 1×10^4 IU/mL to 2×10^5 IU/mL, comprehensive counseling is recommended prior to deciding on oral antiviral prophylaxis.

Systematic reviews show that HBeAg positivity can accurately predict HBV DNA ≥ 2×10^5 IU/mL (specificity: 92.57% [95% CI: 90.04–94.49%]; sensitivity: 88.25% [95% CI: 83.91–91.53%]) in pregnant women.[16] In regions where HBV DNA quantification is not available, HBeAg positivity can serve as an alternative assessment for eligibility for antiviral prophylaxis during pregnancy to prevent MTCT; however, HBV DNA quantification is preferred when feasible. The 2024 WHO guidelines for chronic hepatitis B infection have introduced a conditional recommendation to expand antiviral prophylaxis to all HBsAg-positive pregnant women in settings without access to HBV DNA assays. This may help address the suboptimal uptake and adherence to infant HBV vaccination, particularly the timely administration of the birth dose in highly endemic regions.[17] However, this "prophylaxis-for-all" strategy should be approached cautiously in China, where hepatitis B vaccination is already administered to all infants.

Recommendation 2.4: Antiviral prophylaxis should be initiated between 24 and 28 weeks of gestation to prevent MTCT (1B). For pregnant women with HBV DNA levels ≥ 2×10^5 IU/mL who attend their first prenatal visit after 28 weeks of gestation, antiviral prophylaxis should be initiated immediately (1B).

Rationale: Despite receiving combined immunization with the hepatitis B vaccine and HBIG, infants born to mothers with high viral loads remain at risk for HBV infection. Both a Bayesian network meta-analysis and a systematic review conducted by WHO indicated that the risk of MTCT was lower in pregnant women who receive antiviral prophylaxis before 28 weeks of gestation compared to those who start treatment later in pregnancy.[18,19] Moreover, no significant differences in adverse pregnancy outcomes or birth defect rates were observed between women who initiated antiviral prophylaxis during mid-pregnancy versus late pregnancy.[18,19] In light of this evidence, the 2024 Guidelines recommend starting antiviral prophylaxis at 24 to 28 weeks of gestation for pregnant women at high risk for MTCT. For those with HBV DNA levels ≥ 2×10^5 IU/mL attending their first antenatal visit after 28 weeks, antiviral prophylaxis should be initiated immediately to prevent MTCT.

Recommendation 2.5: TDF (1A) or tenofovir alafenamide (TAF) (1B) is recommended during pregnancy to prevent MTCT.

Rationale: Several randomized controlled trials, cohort studies, and systematic reviews have demonstrated that TDF prophylaxis during pregnancy safely and effectively prevents MTCT without increasing the risk of adverse events, including birth defects.[19–21] Additionally, long-term safety data for infants born to mothers who received TDF during pregnancy had been established.[22] Therefore, TDF prophylaxis is recommended for pregnant women with high HBV viremia to prevent MTCT.

TAF, recognized as a first-line antiviral agent in guidelines for chronic HBV and HIV infections, is supported by emerging evidence regarding its safety and efficacy in preventing HBV MTCT.[23–28] A recent systematic review found no significant differences in the efficacy and safety profiles of TAF and TDF for preventing HBV MTCT.[29] Another systematic review of pregnant women receiving TAF treatment for HBV or HIV infection showed that TAF does not increase the risk of birth defects or negatively affect infant growth compared to TDF.[30] The Antiretroviral Pregnancy Registry (APR) reported the birth outcomes of 1,086 infants born to mothers receiving oral TAF, with approximately 80% of these cases having received TAF since early pregnancy. The registry found a birth defect rate of 3.9% (95% CI: 2.80–5.19%),[31] comparable to the general birth defect rate in China (5.6%) and slightly higher than that reported by the Metropolitan Atlanta Congenital Defects Program in the United States (2.72%).[32] Given these findings, the 2024 Guidelines recommend TAF for pregnant women at high risk of MTCT.

Clinical Question 3: How to manage an unplanned pregnancy in women with chronic HBV infection undergoing antiviral treatment?

Recommendation 3: For women who experience an unplanned pregnancy while on antiviral treatment, TDF treatment can be continued (1B), TAF treatment may be continued after discussing potential safety concerns with the women (2B), and entecavir (ETV) should be switched to TDF treatment (2B). Women with osteoporosis, renal impairment, or high-risk factors for these conditions should consider TAF treatment (2B).

Rationale: Concerns regarding the risk of birth defects associated with antiviral agents are common among pregnant women and clinicians. Currently, there is no evidence to suggest that these antiviral agents increase the risk of birth defects. The APR website has reported pregnancy outcomes for 23,283 women receiving antiviral therapy for HIV or chronic HBV infection, revealing birth defect rates of 3.9% for infants born to mothers treated with TAF and 2.58% for those treated with TDF during early pregnancy.[31] In comparison, the birth defect rate is reported to be 5.6% in the *Report on Prevention and Control of Birth Defects in China (2012)* and 2.72% in the Metropolitan Atlanta Congenital Defects Program in the United States.[32]

Pregnant women who began TDF treatment prior to pregnancy exhibited no significant differences in pregnancy complications or neonatal birth defects compared to untreated groups,[33,34] leading to a recommendation to continue TDF

treatment during pregnancy. For pregnant women who initiate TAF treatment in early pregnancy, the incidence of common pregnancy complications—including gestational hypertension, gestational diabetes, and premature rupture of membranes—was similar to those observed in the TDF group.[26,28] Additionally, the growth and development of infants born to these women align with the growth standards set by China and WHO.[26,28] Based on these findings and APR data, antiviral regimens can be safely and effectively continued for women who begin TAF treatment before conception (following consultation).

Observational studies and APR data indicate a birth defect rate of approximately 3.0% in infants born to women exposed to ETV during early pregnancy.[35,36] Therefore, it is recommended that those who become pregnant while on ETV switch to TDF treatment. However, TDF treatment carries a potential risk of renal impairment and osteoporosis.[37,38] Randomized controlled trials and real-world studies have shown that TAF is superior to TDF concerning bone metabolism and renal safety.[39] Consequently, TAF is an appropriate treatment option for pregnant women with existing osteoporosis or renal impairment, or those at high risk for these conditions.

Clinical Question 4: How to manage chronic HBV-infected pregnant women with abnormal liver chemistries?

Recommendation 4: For HBV-infected pregnant women with abnormal liver chemistries, TDF or TAF treatment should be initiated after ruling out other causes (1B).

Rationale: For women with chronic HBV infection who intend to become pregnant or who are at their first prenatal visit, it is essential to conduct HBV serological marker testing, HBV DNA quantification, liver biochemical tests, and abdominal ultrasound to assess their infection status as early as possible. A prospective cohort study indicated that approximately 10% of pregnant women had elevated ALT levels, regardless of whether they were receiving antiviral prophylaxis, with most patients recovering spontaneously and severe hepatitis being rare.[40] In accordance with the Chinese *Guidelines for the Prevention and Treatment of Chronic Hepatitis B (version 2022)*[11] and the latest safety data for TDF[19] and TAF[28,29] in pregnant women, the 2024 Guidelines recommend initiating TDF or TAF treatment in chronic HBV-infected pregnant women with abnormal liver chemistries after excluding other potential factors. For pregnant women with severe liver fibrosis or early-stage cirrhosis, antiviral treatment should be initiated immediately, regardless of ALT levels.

Clinical Question 5: How to manage parturient who received antiviral treatment during pregnancy?

Recommendation 5: For women who meet antiviral treatment criteria of chronic HBV infection before or during pregnancy, it is recommended to continue antiviral treatment and postpartum follow-up monitoring (1B). For those who do not meet the criteria but received prophylactic antiviral therapy to prevent MTCT, discontinuing treatment immediately after delivery and up to three months postpartum does not increase the risk of liver biochemical abnormalities. Women who discontinue treatment should undergo close monitoring of liver biochemical parameters and HBV DNA levels (1B). If significant declines in HBV DNA and HBeAg levels occur during antiviral prophylaxis, and continued treatment is anticipated to be effective, postpartum antiviral treatment can be resumed (1B).

Rationale: Women who meet the criteria for antiviral treatment before or during pregnancy should continue their treatment and follow-up postpartum. Due to postpartum changes in immune function and hormone levels, approximately 20% of women may experience elevated ALT levels, peaking at three to four weeks and again at nine to twelve weeks postpartum, regardless of HBV infection.[41] Most elevations in ALT are mild to moderate and typically occur within 24 weeks postpartum.[40,41] Systematic reviews indicated that pregnant women with chronic HBV infection were at risk for ALT abnormalities postpartum, regardless of whether they received antiviral treatment, with no significant difference observed between treated and untreated groups.[42] Observational studies and network meta-analyses showed no significant difference in the rates of liver biochemical abnormalities when antiviral prophylaxis was discontinued immediately after delivery up to three months postpartum.[43–46] During the follow-up period after discontinuation, monitoring of liver biochemical parameters and HBV DNA levels every four to six weeks is recommended, and antiviral therapy should be reinitiated if treatment criteria are met during follow-up.

Studies suggested that postpartum changes in cellular immunity in women with chronic HBV infection could lead to hepatitis activity and immune clearance, potentially resulting in higher rates of HBeAg clearance and seroconversion if antiviral therapy was continued.[47,48] Women who maintain TDF treatment postpartum tend to experience faster declines in HBsAg and HBeAg levels.[49] Those with significant declines in HBV DNA and HBeAg levels during pregnancy were likely to achieve higher rates of HBeAg clearance and seroconversion with continued postpartum treatment; some may even achieve HBsAg clearance.[50,51] Consistent with the *Management Algorithm for Prevention of Mother-to-Child Transmission of Hepatitis B Virus (2021)*,[10] the 2024 Guidelines recommend that parturient who experience a significant antiviral-induced decrease in HBV DNA and HBeAg levels during pregnancy continue antiviral treatment postpartum.

Clinical Question 6: Can mothers with chronic HBV infection breastfeed postpartum?

Recommendation 6: Breastfeeding is encouraged after newborns receive combined immunization with both the hepatitis B vaccine and HBIG (2B). It is also advised for mothers on TDF or TAF treatment (2C).

Rationale: Although HBsAg and HBV DNA have been detected in breast milk, breastfeeding does not increase the risk of MTCT.[52,53] Given the substantial benefits of breastfeeding for both mother and infant, infants born to mothers with chronic HBV infection can be breastfed after receiving combined immunization.

Concerns regarding the safety of breastfeeding while on antiviral medication are common among clinicians. Both TDF and TAF are prodrugs of tenofovir, which are quickly absorbed and converted to tenofovir in the intestines, where it exerts its antiviral effects. Tenofovir is minimally absorbed from the gastrointestinal tract. Regardless of whether the mother was treated with TDF or TAF, the drug exposure in infants through breastfeeding was far below the safe relative dose range (5–10%).[54–56] Based on the available evidence and pharmacokinetic data, mothers continuing TDF or TAF treatment postpartum can safely breastfeed.

Clinical Question 7: When should the immune response to immunoprophylaxis be evaluated in infants born to mothers with chronic HBV infection?

Recommendation 7: It is recommended to measure anti-HBs levels one to two months after completing the full immunization schedule to evaluate the immune response in infants

born to mothers with chronic HBV infection (1B).

Rationale: Postpartum immunization with the hepatitis B vaccine and HBIG is crucial in preventing HBV MTCT. Serological testing after immunization provides direct evidence for evaluating the immune response. One study monitoring anti-HBs levels in infants born to mothers with chronic HBV infection found a non-response rate of approximately 1% (0.7–1.6%) at one to six months post-vaccination, which increased to 5.7% at seven to eight months.[57] Additionally, anti-HBs levels gradually decline, with a more significant decrease observed at seven to eight months post-immunization.[57] To identify non-responders early, it is recommended to measure anti-HBs levels one to two months after completing the full immunization schedule.

Clinical Question 8: Is booster immunization required for infants born to mothers with chronic HBV infection?

Recommendation 8: Infants born to mothers with chronic HBV infection, even if they have successfully avoided MTCT, remain at risk for future HBV infection. It is recommended to monitor anti-HBs levels dynamically and to determine the need for booster immunization based on the results (1B).

Rationale: Anamnestic responses induced by the primary hepatitis B vaccine series have been confirmed by long-term follow-up studies. For example, follow-up data from the general population in Alaska, USA, revealed that 47.5% of individuals had anti-HBs levels ≥ 10 mIU/mL 35 years after receiving the plasma-derived hepatitis B vaccine.[58] Among this cohort, 86% retained a protective response after those with anti-HBs levels <10 mIU/mL received a booster dose of the hepatitis B vaccine.[58]

Infants born to mothers with chronic HBV infection remain at risk for HBV infection due to close contact with their mothers, even if MTCT is initially prevented. A prospective study following infants born to mothers with chronic HBV infection until the age of five years found an HBV infection rate of 6.83% (31/454). This rate was significantly lower in children who received booster immunization compared to those who did not (0.50% vs. 11.90%, $p < 0.001$).[59] Therefore, dynamic monitoring of anti-HBs levels in these infants is recommended. For those who do not respond to the initial three-dose hepatitis B vaccine series (HBsAg negative, anti-HBs negative or <10 mIU/mL), a repeat vaccination series following the "0-1-6 month" schedule is suggested, with anti-HBs levels measured one to two months after the repeat series. Some experts recommend timely booster immunization before two years of age for infants born to HBeAg-positive mothers or those with low anti-HBs levels at seven months of age, rather than waiting for their anti-HBs levels to become negative.

Clinical Question 9: Does chronic HBV infection increase the risk of adverse pregnancy outcomes in infertile women undergoing assisted reproductive technology (ART)? Does ART increase the risk of MTCT of HBV?

Recommendation 9: Chronic HBV infection does not affect the rates of good-quality embryos, clinical pregnancies, or live births in infertile women undergoing ART (2B). Furthermore, it does not increase the incidence of gestational diabetes, gestational hypertension, premature rupture of membranes, or low birth weight in newborns (2B). The use of ART in infertile women with chronic HBV infection does not elevate the risk of MTCT (2C).

Rationale: Previous studies have indicate that there are no significant differences in fertilization rates, cleavage rates, good-quality embryo rates, implantation rates, clinical pregnancy rates, live birth rates, or miscarriage rates between infertile women with chronic HBV infection and HBsAg-negative infertile women.[60,61] Furthermore, among pregnant women with chronic HBV infection undergoing ART, the incidence of gestational diabetes, gestational hypertension, and premature rupture of membranes does not differ from that of non-HBV-infected pregnant women, nor does the risk of low birth weight in neonates.[60,61]

Observational cohort studies showed that infants born to women with chronic HBV infection who underwent ART and received combined immunization were HBsAg negative at nine to fifteen months of age.[62,63] Therefore, infertile women with chronic HBV infection can proceed with ART as usual. There is no evidence to suggest that ART in infertile women with high HBV DNA levels increases the risk of MTCT.

Clinical Question 10: Do invasive procedures increase the risk of MTCT in pregnant women with chronic HBV infection?

Recommendation 10: Pregnant women with chronic HBV infection who require amniocentesis can safely undergo the procedure (1B). However, for those with HBV DNA levels ≥ 1×10^7 IU/mL or HBeAg positivity, amniocentesis increases the risk of intrauterine infection (1B). If obstetric conditions permit, it is recommended to initiate antiviral prophylaxis during the window period prior to amniocentesis to reduce the risk (2C).

Rationale: The risk of MTCT of HBV during invasive prenatal procedures such as amniocentesis, chorionic villus sampling, and cordocentesis is a significant concern for pregnant women with chronic HBV infection and their obstetricians. A systematic review showed that the risk of MTCT was associated with HBV DNA levels in women undergoing amniocentesis.[64] Specifically, the risk increases 6.26-fold in women with HBV DNA ≥ 1×10^7 IU/mL and 2.25-fold in HBeAg-positive women.[64] Therefore, pregnant women with HBV DNA ≥ 1×10^7 IU/mL or HBeAg positivity should be informed of the heightened risk of MTCT associated with amniocentesis. Considering the expanding indications for antiviral therapy, growing safety evidence regarding antiviral medications during pregnancy, and the broad time window for amniocentesis (18 to 22^{+6} weeks of gestation), initiating TDF or TAF antiviral prophylaxis during the window period before the procedure should be discussed thoroughly with the patient and their family to reduce the potential risk of MTCT. Currently, there are no recommendations regarding whether chorionic villus sampling and cordocentesis increase the risk of MTCT of HBV.

Research Gaps

1. Long-term Safety of Infants Born to Mothers Treated with TAF. Data on the long-term safety of infants born to mothers treated with TAF for chronic HBV infection still need to be accumulated.

2. Postpartum Antiviral Regimen and Outcome Evaluation. Postpartum changes in immune status and hormone levels can affect cellular immune function, potentially leading to hepatitis activity, which may represent a distinctive "immune active stage". Future research should focus on optimizing and evaluating the effectiveness of postpartum antiviral therapy.

3. Effectiveness and Cost-Effectiveness of MTCT Prevention without HBIG. The current standard strategy for preventing HBV MTCT in China includes postpartum administration of the hepatitis B vaccine and HBIG. However, the high cost and logistical requirements of maintaining a cold chain for HBIG limit its accessibility in underdeveloped regions. On-

going studies are investigating the effectiveness of antiviral prophylaxis during pregnancy combined with infant hepatitis B vaccination, without HBIG.

4. Long-term Safety of Infants Exposed to Antiviral Therapy Throughout Pregnancy. As the indications for antiviral therapy expand, the number of infants exposed to antiviral drugs throughout pregnancy will increase. Current safety data on these infants are limited, and follow-up periods are relatively short. It is essential to establish long-term follow-up cohorts for pregnant women with chronic HBV infection and their offspring to provide more scientific evidence on the safety of antiviral agents for mothers and children.

5. Risk of HBV Transmission Through Germ Cells. Previous studies have detected HBV markers in oocytes, spermatocytes, and zygotes. While combined antiviral prophylaxis during pregnancy and postpartum immunization have reduced the MTCT rate to approximately 0.3%, the probability of HBV transmission through germ cells is presumed to be very low but requires further clarification.

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Conflict of interest

All experts signed a conflict-of-interest declaration form before joining the 2024 Guidelines committee. No conflicts of interest related to the 2024 Guidelines exist. HR has been an Editor-in-Chief of *Journal of Clinical and Translational Hepatology* since 2013, FJ have been an Editorial Board Member of *Journal of Clinical and Translational Hepatology* since 2023. The other authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (YZ, LL, WZ, HR), drafting of the manuscript (JL, QZ, FJ), critical revision of the manuscript for important intellectual content (YZ, LL, WZ, HR), administrative and study supervision (YZ, LL, WZ, HR). All authors have read and approved the final version and publication of the manuscript.

Declaration of revision and update of the 2024 Guidelines

The update of the 2024 Guidelines was initiated and developed by the Infectious Disease Physicians Branch of the Chinese Medical Doctor Association and the Chinese Society of Infectious Diseases of the Chinese Medical Association, with methodological support from the Chinese GRADE Center/Institute of Health Data Science at Lanzhou University. The update process followed the *Guiding Principles for the Formulation/Revision of Clinical Diagnosis and Treatment Guideline in China (2022 Edition)* issued by the Chinese Medical Association.[65] The 2024 Guidelines had been registered on the International Practice Guidelines Registry Platform (http://www.guidelines-registry.org/, PREPARE-2023CN171). Readers are invited to contact the registration platform or the Guideline working group for the protocol if needed.

Before updating the 2024 Guidelines, we conducted a literature search (from the last guidelines' literature search cutoff date in December 2018 to December 2023), a questionnaire survey, and other assessments to evaluate the effectiveness of the first version's recommendations and identify the new clinical issues that needed to be addressed. The working group for the 2024 Guidelines utilized a convenience sampling method to survey healthcare workers engaged in HBV MTCT prevention, collecting 156 valid questionnaires from 22 hospitals. We also referenced HBV MTCT prevention guidelines published in articles and conference abstracts from PubMed, Embase, the Cochrane Library, and three Chinese literature databases (CNKI, WanFang, and CBM) and conducted three new systematic reviews. Finally, we summarized all relevant information and presented it to the expert group for decision-making. In updating the recommendations, the expert group considered the following aspects: 1) whether new evidence alters the risk-benefit ratio; 2) whether there is a need to change the strength of the recommendations; and 3) the applicability, clarity, and accuracy of previous recommendations. Consistent with the process used for the 2019 Guidelines, the GRADE system was employed to determine the certainty of the evidence, and consensus was achieved through three rounds of Delphi voting. The draft recommendations were then sent to external review experts for evaluation. The Steering Committee approved the final recommendations based on the feedback received during the external review process, resulting in the final version of the 2024 Guidelines.

The recommendations reported adhere to the requirements of the *Checklist for the Reporting of Updated Clinical Guidelines*[66] and the *Standards for Reporting Items for Health Care Practice Guidelines*.[67]

The 2024 Guidelines Steering Committee

The working group of the 2024 Guidelines consisted of an Expert Panel and an Evidence Assessment Team comprising 54 experts specializing in infectious diseases, hepatology, obstetrics and gynecology, and evidence-based medicine, including one methodologist.

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