Hong Kong J Gynaecol Obstet Midwifery 2021;21(1):49-52 | https://doi.org/10.12809/hkjgom.21.1.07

# Prevention of maternal-to-child transmission of hepatitis B: a narrative review

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Chronic hepatitis B virus (HBV) infection can result in cirrhosis and hepatocellular carcinoma. Most chronic HBV infections are caused by mother-to-child transmission during the perinatal period. The World Health Organization aims to eradicate HBV globally by 2030. Hong Kong has implemented a wide range of preventive strategies to decrease maternal-to-child transmission. This review summarises the experience in Hong Kong and the current recommendations to prevent HBV vertical transmission.

*Keywords: Antiviral agents; Hepatitis B virus; Infectious disease transmission, vertical; Pregnancy; Vaccination*

## Introduction

Around 257 million people have chronic hepatitis B virus (HBV) infection, and around 887 000 people have died from HBV-related complications. Only 10.5% of chronic carriers (27 million people) are aware of their infection[1], and most carriers are unrecognised, with no monitoring or treatment. In Hong Kong, the prevalence of HBV has decreased steadily from 1990 to 2018[2] but remains high (7.8%) according to the territory-wide prevalence study in 2015-2016[3]. HBV infection can be acquired through vertical or horizontal transmission, but the former has a higher chance of progressing to chronic infection. This review focuses on maternal-to-child transmission (MTCT) of HBV and its prevention in Hong Kong.

## Preventive strategies

Hong Kong was once an area of high HBV endemicity. Different preventive strategies have been implemented to bring down its prevalence. Antenatal screening of hepatitis B surface antigen (HBsAg) is performed in all pregnant women, aiming to identify unrecognised chronic carriers. HBV vaccination and hepatitis B immunoglobulin (HBIg) injection to newborns of carrier mothers have been implemented since 1984, and universal neonatal HBV vaccination has been implemented since 1988[4]. The HBV carriage rate has decreased steadily between 1990 and 2018 from 11.3% to 4.5% in the antenatal population and from 9.6% to 4.9% in the premarital check-up population[2].

Aiming to eradicate HBV vertical transmission, triage of women with a high viral load to receive tenofovir disoproxil fumarate (TDF) has introduced in Queen Mary Hospital and Prince of Wales Hospital since January 2020 and has expanded to other units since August 2020. This is in line with the World Health Organization target to decrease the prevalence of HBV infection in children to 0.1% (ie, 90% reduction in the incidence of new HBV infections) by 2030[5-7].

## Knowledge and healthcare pattern

Only around 14% of the adult population in Hong Kong have a good knowledge of HBV infection[8]. Pregnant women in Hong Kong have insufficient knowledge on the modes of transmission, prevention, and possible sequelae of HBV infection[9]. Most pregnant HBV carriers in Hong Kong are not evaluated by a hepatologist during and after delivery (86.4% and 52.6%, respectively), although 91% of them are aware of their HBV carrier status before pregnancy[10]. Pregnancy initiates basic biochemical and virological investigations as well as multidisciplinary care (with hepatologists) for these HBV carriers. Long-term care of these women decreases MTCT by starting antiviral treatment in the third trimester in women with high HBV DNA.

## MTCT and immunoprophylaxis failure

When HBIg or vaccination is not given to the newborns of HBV carriers, the rate of MTCT can be as high as 73%. A completed course of HBV vaccination reduces the MTCT rate to ~21% and further to 2.9% to 6.8% with the addition of birth dose HBIg[11]. Timely administration of HBIg and birth dose HBV vaccine within 1 to 2 hours can reduce the MTCT rate to as low as 0.9% to 2%[12,13].

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Immunoprophylaxis failure (IF) refers to persistent MTCT despite neonatal HBIg and HBV vaccination and is defined by seropositive HBsAg or HBV DNA level at 2 to 3 months after completion of vaccination[14]. The mechanisms of IF include germline infection at conception, maternal blood contamination at the time of prenatal invasive procedures, and contact with maternal secretion during labour. The risk of IF increases with a positive hepatitis B e antigen status and high HBV DNA viral load[15]. The IF rate depends on the provision and the coverage of HBIg and HBV vaccination. Among Hong Kong children aged 2 to 5 years, the coverage of the three doses of HBV vaccination is almost 100%, but the IF rate remains at 1.1%, according to a multicentre study in 2014-2016[2]. Positive hepatitis B e antigen and high HBV DNA viral load of ≥8 $\log_{10}$ copies/mL (≥7.23 $\log_{10}$ IU/mL) at 28 to 30 weeks are predictors of IF[16].

## Maternal antiviral treatment

A high viral load is a predictor of IF. Viral load suppression through antiviral treatment during pregnancy can prevent IF in highly viraemic pregnant women. Lamivudine, telbivudine, and TDF are nucleoside and nucleotide analogues that can be used safely during pregnancy for the prevention of MTCT[17]. TDF is the preferred treatment as it has a high potency and a strong barrier to resistance[18,19]. In a study in China involving 200 HBV carrier mothers with HBV DNA >200 000 IU/mL, daily 300 mg oral TDF from 30 to 32 weeks of gestation significantly lowered maternal HBV DNA at delivery and neonatal infection (intention to treat analysis: 5% vs 18%, p=0.007; per-protocol analysis: 0% vs 7%, p=0.01)[20]. However, a clinical trial in Thailand involving 331 women did not find any significant difference in the rate of IF between women taking TDF or placebo (0 vs 2%, p=0.12)[13]. This negative finding could be related to the low IF in both groups as a result of timely HBIg and vaccination and the inclusion of women with low viral loads[21].

The World Health Organization recommends the use of TDF in women with HBV DNA ≥200 000 IU/mL starting from 28 weeks of gestation until birth or even afterwards[7], in line with other international guidelines[22,23]. Under most circumstances, TDF treatment starting from 28 weeks can adequately suppress viral load before delivery. However, in women at high risk of preterm delivery or with a high baseline HBV DNA of ≥8 $\log_{10}$ IU/mL, TDF may be used in the early second trimester[24]. Early use of TDF should also be considered in women undergoing amniocentesis, as there is an increased risk of MTCT if the HBV DNA is ≥7 $\log_{10}$ copies/mL or ≥7 $\log_{10}$ IU/mL[25,26].

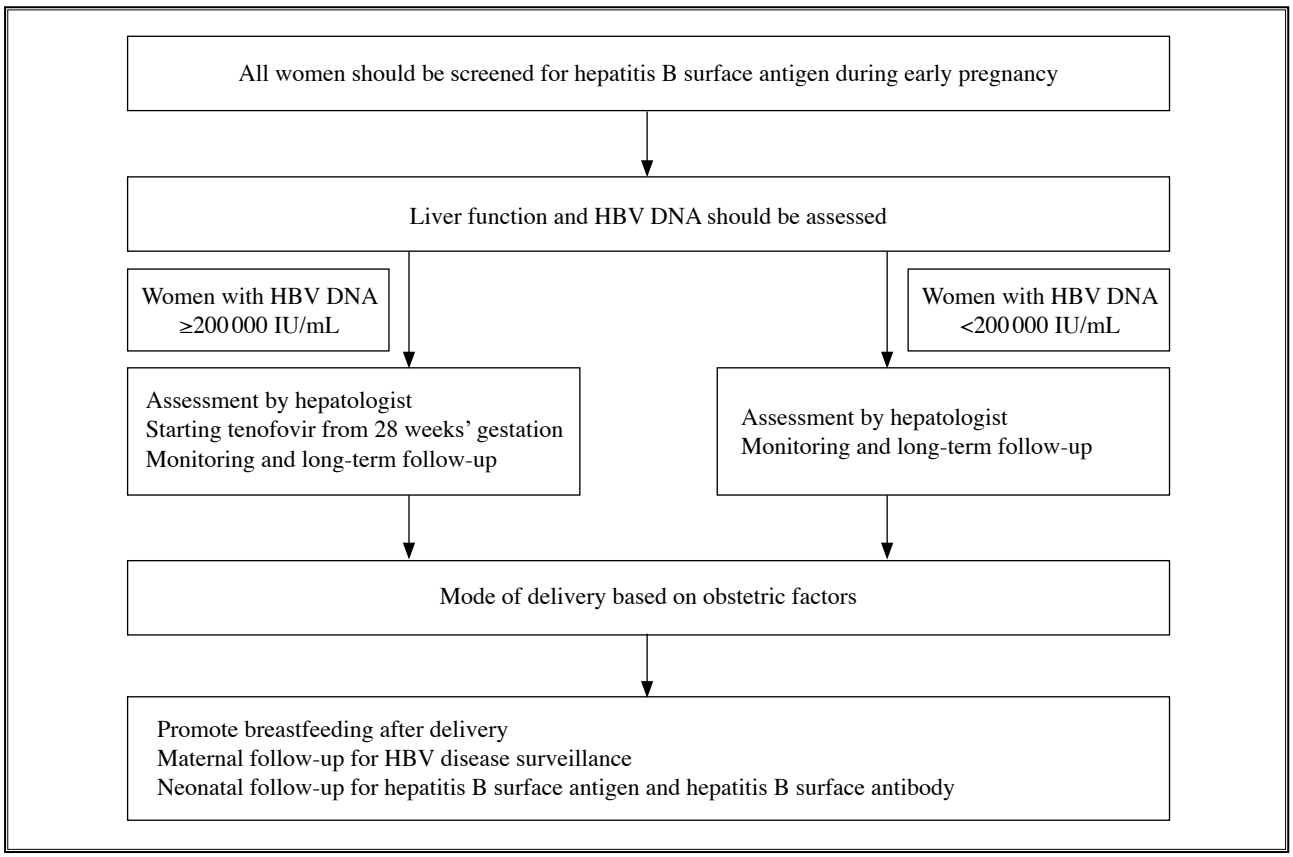


*Figure. Clinical management algorithm for hepatitis B virus (HBV) carriers during pregnancy*

## Role of caesarean section

With timely HBIg and HBV vaccination, the duration of membrane rupture and labour does not affect the IF rate even in women with high viral loads[27]. In a systematic review and meta-analysis involving 18 studies and 11 446 mother-and-child pairs, the rate of IF at the age of 6 months was similar between the vaginal delivery group and the caesarean section group (4.1% vs 3.3%)[28]. Therefore, caesarean section should not be routinely recommended to HBV carriers without obstetrical indications.

## Clinical management algorithm

All women should be screened for HBsAg during early pregnancy. For women with positive HBsAg, liver function and HBV DNA should be assessed. HBV DNA quantification as early as before 22 weeks of gestation can be used reliably to predict the risk of IF and guide the use of antiviral treatment[29]. Women with high HBV DNA (>200 000 IU/mL) should be seen by a hepatologist to discuss the use of TDF after 28 weeks of gestation; whereas women with low HBV DNA should also be reminded to continue with long-term follow-up for surveillance of HBV complications (Figure).

Vaginal delivery should not be restricted, and caesarean section should be reserved for obstetric indications[28]. Hepatic flares can occur in women who stopped TDF after delivery, although they are mostly self-limiting and asymptomatic[13,20]. The timing of stopping TDF treatment post-delivery is controversial[30]; multidisciplinary care can facilitate smooth transfer of care for these women from obstetricians to hepatologists.

Breastfeeding should be promoted in HBV carriers irrespective of TDF use. The dosage of TDF exposed to breastfed infants was 0.01% to 0.04% of the recommended weight-adjusted therapeutic dose in infants (0.5% to 16% of the dosage experienced by fetuses via placental transfer)[31]. Therefore, women should be reassured that there is no contraindication of TDF use during breastfeeding[23,32,33]. For women not taking antiviral treatment, there is also no evidence that breastfeeding in HBV carriers increases the risk of MTCT after neonatal immunisation[34].

## Conclusion

Timely HBIg and neonatal HBV vaccination lowers the IF rate and the prevalence of HBV in Hong Kong. Multidisciplinary care for pregnant carriers increases the awareness and continuation of HBV management after delivery. With prescription of TDF to pregnant carriers with high HBV viral loads, Hong Kong is expected to enter a new era of HBV eradication.

## Declaration

The authors have no conflict of interest to disclose.

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