

# 2024 Hong Kong College of Obstetricians and Gynaecologists guideline on antenatal screening and management of hepatitis B for prevention of mother-to-child transmission

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## ABSTRACT

Hepatitis B virus (HBV) infection remains a global threat and causes a substantial disease burden. The World Health Organization has set a goal to eliminate viral hepatitis as a public health threat by 2030. Mother-to-child transmission (MTCT) is the main route of HBV transmission. Most MTCT cases can be prevented by timely active and passive immunisation at birth, but failed immunoprophylaxis in infants continues to occur among women with a high viral load during pregnancy. Hepatitis B virus disease activity in infected mothers should be assessed during early pregnancy, and multidisciplinary management with antiviral medication should be offered to women with a high viral load. In these guidelines, we present management strategies for HBV-infected pregnant women that are intended to reduce the risk of MTCT in Hong Kong.

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## Introduction

Hepatitis B virus (HBV) infection is a key cause of liver diseases associated with high rates of morbidity and mortality. The World Health Organization (WHO) estimated that in 2019, 296 million people had chronic HBV infections and there were approximately 820 000 HBV-related deaths, mostly due to cirrhosis and hepatocellular carcinoma.<sup>1,2</sup> The estimated global prevalence of HBV infection in 2019 was 3.8%.<sup>1,2</sup> To eliminate viral hepatitis as a public health threat by 2030, the WHO has outlined a set of global impact and service coverage targets, including a prevalence of  $\leq 0.1\%$  for hepatitis B surface antigen (HBsAg) among children 5 years of age; this target will help eliminate mother-to-child transmission (MTCT) of HBV.<sup>3,4</sup>

Prevention is the main strategy for HBV elimination because there is currently no complete cure for HBV. In high endemic regions, MTCT, also referred to as vertical transmission, remains

the primary route of HBV transmission; the risk of chronicity after HBV infection is 90% in the perinatal period, compared with 5% in adulthood.<sup>5</sup> Hepatitis B virus can also be spread through horizontal transmission, especially during early childhood. Pregnancy offers an ideal occasion to eliminate HBV through proper screening and timely treatment for asymptomatic HBV-infected mothers and their infants. Universal timely neonatal hepatitis B vaccination is the most important intervention for reducing MTCT of HBV. The administration of hepatitis B immunoglobulin (HBIG) for infants born to HBV-infected mothers, as well as maternal peripartum prophylaxis with antivirals, would provide additional protection against MTCT of HBV.

In these guidelines, we focus on the management of HBV-infected pregnant women for reduction of MTCT risk, which is a core strategy in the Hong Kong Viral Hepatitis Action Plan 2020–2024.<sup>6</sup>

## Prevention of mother-to-child transmission by active and passive immunisation

### Evidence to support active and passive immunisation

Neonatal hepatitis B vaccination remains the most effective measure for prevention of MTCT; it can reduce the rate of MTCT from 90% to 21% in hepatitis B e antigen (HBeAg)-positive women and from 30% to 2.6% in HBeAg-negative women.<sup>7</sup> The addition of a birth dose of HBIG can further reduce the risk to 6% in HBeAg-positive women and 1% in HBeAg-negative women.<sup>7</sup> A delayed birth dose of hepatitis B vaccination and failed administration of HBIG at birth have been associated with immunoprophylaxis failure (IF) [see below].<sup>8</sup>

In Hong Kong, infants born to HBV-infected mothers have received hepatitis B vaccination and HBIG since 1984. Neonatal vaccination was extended to all infants, regardless of their mothers' HBV infection status, in 1988. The implementation of a universal childhood hepatitis B vaccination programme has led to a continuous reduction in HBV prevalence in Hong Kong, achieving coverage rates of >99% for the birth dose, as well as the second and third doses of vaccine.<sup>9</sup> Thus, HBsAg prevalence among the antenatal population in Hong Kong gradually decreased from 10.8% in 1992 to 2.5% in 2022.<sup>10</sup>

### Recommendations of the World Health Organization

The WHO recommends the followings<sup>11-13</sup>:

- All pregnant women should undergo HBsAg testing at least once, as early in their pregnancy as possible.
- All infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours after delivery.
- The birth dose should be followed by two or three doses to complete the primary vaccination series.

### Recommendations of the Hong Kong College of Obstetricians and Gynaecologists

The Hong Kong College of Obstetricians and Gynaecologists (HKCOG) recommends the followings:

- All pregnant women should undergo HBsAg screening in early pregnancy.
- All infants should receive the birth dose of hepatitis B vaccine as soon as possible (within 24 hours after delivery), followed by the second and third doses at 1 month and 6 months of age, respectively.
- Infants born to HBV-infected mothers should receive the birth dose of HBIG when they receive the birth dose of hepatitis B vaccine.

## 香港婦產科學院2024年指引：產前篩查與治理 乙型肝炎預防母嬰傳播

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乙型肝炎病毒感染仍然是全球性威脅，帶來沉重的疾病負擔。世界衛生組織訂下在2030年或之前消除病毒性肝炎作為公共衛生威脅的目標。母嬰傳播是傳播乙型肝炎病毒的主要途徑。嬰兒出生後及時的主動和被動免疫能預防大多數母嬰傳播，但新生兒免疫預防失敗的情況仍然會在妊娠期病毒載量較高的孕婦中出現。受感染的孕婦應在懷孕早期接受乙型肝炎病毒活躍評估，而病毒載量較高的孕婦應接受跨學科治理及服用抗病毒藥物。本指引介紹香港針對受乙型肝炎病毒感染的孕婦之處理，以減低母嬰傳播的風險。

## Immunoprophylaxis failure

### Definition and prevalence

Among infants who undergo active and passive immunisation for hepatitis B, some do not develop adequate antibodies. Immunoprophylaxis failure is defined as persistent HBsAg seropositivity in infants when tested at the ages of 9 to 12 months, or 1 to 2 months after completion of the vaccination series.<sup>14</sup> The reported rates of IF range from 1% to 9% in the literature.<sup>15</sup> In Hong Kong, a single-centre study revealed an IF rate of 2.5% (3/121) in 2001.<sup>16</sup> Another prospective study involving five maternity units in Hong Kong showed that the IF rate was 1.1% (7/641) between 2014 and 2016.<sup>17</sup>

### Possible mechanisms

The possible mechanisms of IF are outlined in Figure 1.<sup>18</sup> Germline infection is a possibility because HBV DNA has been detected in sperm and ova of people with HBV infection, as well as embryos from male HBsAg-positive/female HBsAg-negative couples or male HBsAg-negative/female HBsAg-positive couples.<sup>19-21</sup> Transplacental infection is another possible mechanism of IF. The gradual decreases in the detection rates of HBV markers and layers of affected placental cells from the maternal side to the fetal side support the hypothesis that progressive HBV placental infection could lead to in utero infection.<sup>22,23</sup> Additionally, invasive prenatal tests can cause HBV inoculation from maternal blood, especially in HBsAg-positive pregnant women with a high viral load. A retrospective cohort study showed that the risk of IF after amniocentesis was higher in women with an HBV DNA level of  $\geq 7 \log_{10}$  IU/mL than in women with an HBV DNA level of  $< 7 \log_{10}$  IU/mL (10.8% vs 0%;  $P=0.004$ ).<sup>24</sup> During vaginal delivery, contact with vaginal secretions harbouring HBV may also increase the risk of

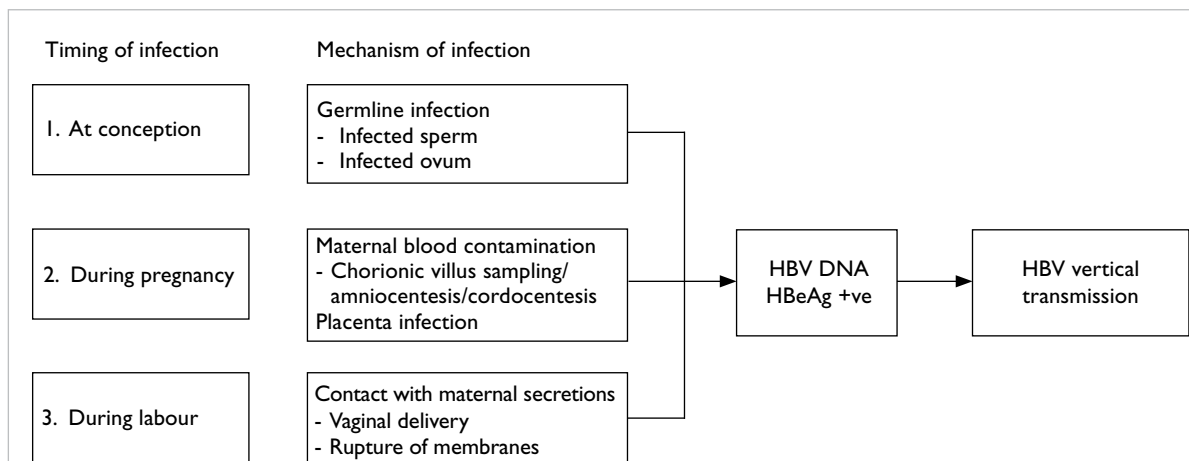


FIG 1. Mechanisms of immunoprophylaxis failure<sup>18</sup>

Reprinted from *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 169(1), KW Cheung, MTY Seto, SF Wong, Towards complete eradication of hepatitis B infection from perinatal transmission: review of the mechanisms of in utero infection and the use of antiviral treatment during pregnancy, 17-23, Copyright 2013, with permission from Elsevier

Abbreviations: +ve = positive; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus

vertical transmission. Thus, a delay in vaccination to infants at birth increases the risk of IF.

### Risk factors

The risk of IF mainly depends on the degree of viral replication, any invasive prenatal procedures, and the availability and timing of the birth dose vaccine and HBIG. Immunoprophylaxis failure is strongly correlated with the viral load (ie, DNA level) in maternal blood during the antenatal and perinatal periods.<sup>21,25</sup> Although non-infectious HBeAg is produced during viral replication, it is associated with high HBV DNA levels. Thus, both maternal HBeAg-positive status and a high maternal HBV DNA level are risk factors for IF.<sup>17,26,27</sup> In a multicentre study involving 641 women and 654 infants in Hong Kong, all seven cases of IF were born to HBeAg-positive mothers with an HBV DNA level of  $>7.2 \log_{10}$  IU/mL.<sup>17</sup> To reduce the maternal viral load and the risk of IF, maternal use of antivirals as peripartum prophylaxis should be considered.

## Antenatal antiviral prophylaxis to prevent immunoprophylaxis failure

### Evidence of the effectiveness of antenatal antiviral treatment

Immunoprophylaxis failure occurs in infants of highly viraemic mothers despite timely birth doses of hepatitis B vaccine and HBIG. Similar to human immunodeficiency virus and herpes simplex virus, antenatal antiviral treatment can suppress the viral load and reduce the risk of MTCT.<sup>28,29</sup>

A randomised controlled trial involving 200

HBsAg-positive pregnant women showed that daily oral intake of 300-mg tenofovir disoproxil fumarate (TDF) from 30 to 32 weeks of gestation could significantly lower maternal HBV DNA at delivery and thus reduce the rates of IF (intention-to-treat analysis: 5% vs 18%,  $P=0.007$ ; per-protocol analysis: 0% vs 7%,  $P=0.01$ ).<sup>30</sup> Although a subsequent multicentre, double-blinded, randomised controlled trial involving 331 women did not show any significant difference in the rate of IF between women receiving TDF and placebo beginning at 28 weeks of gestation (0 vs 2%;  $P=0.12$ ), the zero MTCT rate in the TDF group confirmed the efficacy of TDF intake.<sup>31</sup> The inclusion of women with lower viral loads and the timely administration of hepatitis B vaccine and HBIG (median time: approximately 1.3 hours after birth) might explain the comparable IF rates between the TDF and placebo groups.<sup>32</sup>

In a meta-analysis, the pooled odds ratios derived from randomised controlled trials of the efficacy of peripartum antiviral prophylaxis for reducing MTCT risk were 0.10 for TDF (95% confidence interval [CI]=0.03-0.35), 0.16 for lamivudine (95% CI=0.10-0.29), and 0.14 for telbivudine (95% CI=0.09-0.21).<sup>33</sup> Although these three antivirals are highly effective in preventing MTCT and can be safely used during pregnancy without maternal or infant safety concerns, TDF is recommended because it has a high threshold for drug resistance.<sup>11,33,34</sup>

### World Health Organization and international recommendations

According to the WHO, pregnant women who test positive for HBV infection (ie, HBsAg-positive)

and have an HBV DNA level of  $\geq 5.3 \log_{10}$  IU/mL ( $\geq 200\,000$  IU/mL) should receive TDF prophylaxis from the 28th week of pregnancy until birth or later to prevent MTCT of HBV. This prophylaxis should be provided along with the three-dose hepatitis B vaccination for infants, including a timely birth dose.<sup>11</sup> This recommendation is consistent with clinical guidelines from other international bodies including the American Association for the Study of Liver Diseases (AASLD),<sup>35</sup> the European Association for the Study of the Liver,<sup>36</sup> and the Asian Pacific Association for the Study of the Liver (Table).<sup>37</sup> Some experts have also suggested initiation of TDF early in the second trimester for individuals with a high risk of preterm birth or an HBV DNA level of  $\geq 8 \log_{10}$  IU/mL ( $\geq 100\,000\,000$  IU/mL).<sup>15</sup>

### Use of antenatal antiviral treatment to prevent immunoprophylaxis failure in Hong Kong

To further reduce the risk of MTCT of HBV, since August 2020, all birthing hospitals under the Hospital Authority have been referring HBV-infected pregnant women with a high HBV viral load (ie, an HBV DNA level of  $>200\,000$  IU/mL) to hepatology clinics and hepatitis nurse clinics for assessment and consideration of initiating antiviral prophylaxis by the third trimester. Other HBV-infected pregnant women are also referred to the appropriate level of

care for routine HBV management.

### Recommendations of the Hong Kong College of Obstetricians and Gynaecologists

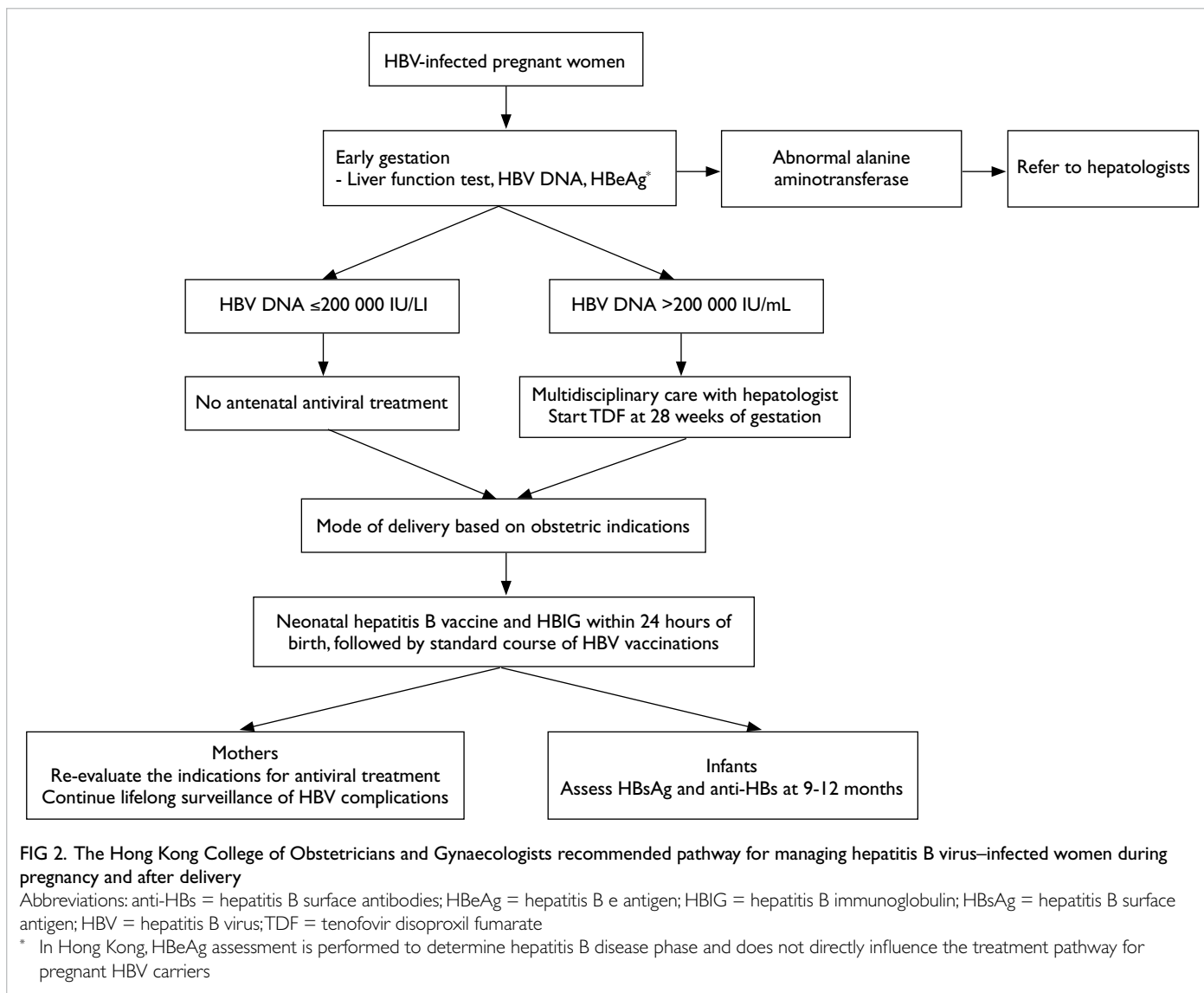
The HKCOG recommends the followings (Fig 2):

- Hepatitis B virus–infected pregnant women should undergo assessments of HBV DNA level, HBeAg status, and baseline liver function in early pregnancy to determine the need for antiviral prophylaxis to prevent MTCT of HBV and the need for antiviral treatment to manage maternal indications.<sup>38–40</sup>
- There is no need for repeat HBV DNA quantification in later stages of pregnancy. Hepatitis B virus DNA levels typically remain stable during pregnancy and similar cut-offs could be used to predict the risk of IF.<sup>40</sup>
- For women with an HBV DNA level of  $>5.3 \log_{10}$  IU/mL ( $>200\,000$  IU/mL), multidisciplinary care involving hepatologists is advised to discuss the indications and safety of antenatal TDF to reduce the risk of IF.<sup>11</sup>
- For women with an HBV DNA level of  $\leq 5.3 \log_{10}$  IU/mL ( $\leq 200\,000$  IU/mL), reminders should be established for long-term regular monitoring and follow-up after delivery, in accordance with established protocols for patients with chronic HBV infection.<sup>34,41</sup>

TABLE. Recommendations from various guidelines for initiating antiviral treatment (tenofovir disoproxil fumarate) to prevent immunoprophylaxis failure

Organisation	Viral load to consider antiviral treatment, IU/mL	Gestational age to begin antiviral treatment, wk	Mode of delivery	Antiviral treatment after delivery	Breastfeeding
WHO <sup>11</sup>	$\geq 200\,000$	28	Not specified	Continue at least until birth	Not contraindicated in women receiving TDF
AASLD <sup>35</sup>	$>200\,000$	28–32	Caesarean section is not indicated	May stop after delivery or continue until 12 weeks postpartum	Not contraindicated in women receiving antiviral treatment
EASL <sup>36</sup>	$>200\,000$	24–28	Caesarean section is not recommended for reducing the risk of HBV mother-to-child transmission in HBsAg-positive women, but it may be recommended for Asian HBeAg-positive women with a high HBV DNA level ( $>6.14 \log_{10}$ IU/mL) who did not receive antiviral therapy during pregnancy	Continue until 12 weeks after delivery	Not contraindicated in women receiving TDF
APASL <sup>37</sup>	$\geq 200\,000$	24–28	Caesarean section should not be performed solely to reduce the risk of vertical transmission	May stop after delivery or continue until 12 weeks postpartum	Not contraindicated in women receiving TDF
HKCOG	$>200\,000$	28	Mode of delivery based on obstetric indications	At least until birth, then review the need to continue antiviral treatment after delivery	Not contraindicated in women receiving TDF

Abbreviations: AASLD = American Association for the Study of Liver Diseases; APASL = Asian Pacific Association for the Study of the Liver; EASL = European Association for the Study of the Liver; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HKCOG = Hong Kong College of Obstetricians and Gynaecologists; TDF = tenofovir disoproxil fumarate; WHO = World Health Organization



## Antenatal management and the mode of delivery

There is conflicting evidence regarding the associations of HBV infection with adverse pregnancy outcomes. The results of some studies have suggested an increased risk of gestational diabetes and preterm birth,<sup>42-47</sup> whereas the results of other studies have not supported this association.<sup>48-50</sup> More data are needed to evaluate the impacts of viral load on pregnancy complications, but the available evidence does not warrant additional antenatal surveillance. Although there is a theoretical risk of intrauterine HBV exposure after chorionic villus sampling, fetal scalp blood sampling, and the use of fetal scalp electrodes, data concerning the risk of vertical transmission after these procedures are scarce. The effects of viral load on these procedures are also unknown, but the risk of vertical transmission is likely to be smaller in women with a lower viral load. Women

should be counselled about this limited evidence, and these procedures generally should be avoided. For amniocentesis, the risk of IF is low when the viral load is  $<7 \log_{10}$  IU/mL. In one study, transplacental amniocentesis did not increase the rate of IF, but this finding was based on a small number of cases.<sup>51</sup> A reasonable approach comprises implementing transamniotic amniocentesis while avoiding transplacental puncture. Caesarean delivery should not be offered solely to prevent MTCT of HBV, and the mode of delivery should be based on obstetric indications.

## Breastfeeding, maternal follow-up, and neonatal follow-up after delivery

Breastfeeding is not contraindicated for mothers who continue to receive TDF. Although a low level of TDF can be detected in breast milk, there



is no evidence that this low level leads to adverse outcomes.<sup>35</sup> Infants should receive a routine three-dose course of hepatitis B vaccination at birth, 1 month of age, and 6 months of age.

The WHO emphasises the need for post-vaccination serological testing (PVST) of infants born to HBsAg-positive mothers.<sup>12</sup> This testing includes testing of antibodies to HBsAg, as well as HBsAg itself, at 9 to 12 months of age (or 1 to 2 months after the final dose of the vaccine series, if the series is delayed).<sup>14</sup> It allows vaccine non-responders to receive a booster dose of vaccine to reduce the risk of horizontal transmission. Additionally, infants with IF should be monitored by healthcare professionals to identify liver conditions and potential complications (eg, cirrhosis and hepatocellular carcinoma).<sup>52</sup> Finally, it can provide valuable information concerning the effectiveness of MTCT prevention strategies.

The Department of Health and the Hospital Authority established a collaboration to provide a PVST service, initiated in January 2022, for infants born to HBV-infected mothers in April 2021 or later; covered infants must attend the Maternal and Child Health Centres of the Department of Health. Beginning in June 2022, mop-up PVST was arranged for infants born in or after October 2020; testing completion was required before the age of 24 months. Blood collection for PVST is conducted in Hong Kong Children's Hospital at 9 to 12 months of age, and up to the age of 24 months (or 1 to 2 months after the final dose of hepatitis B vaccine), to identify HBV-infected infants and infants with an inadequate immune response to the primary series of hepatitis B vaccine; these infants are eligible for re-vaccination. Hepatitis B virus-infected infants are referred to paediatric units within the Hospital Authority for management. Infants who have an inadequate or absent immune response after the second course of hepatitis B vaccine are referred to the Hong Kong Children's Hospital for further assessment.

Lack of continuity of care has been common in Hong Kong; for example, 52.6% of HBV-infected individuals did not receive any medical care within 1 year after delivery.<sup>53</sup> Mothers with chronic HBV infection should undergo regular monitoring of disease activity and surveillance of HBV complications, in accordance with established protocols for patients with chronic HBV infection.<sup>34,41</sup>

## Indications for and duration of continued antiviral treatment after delivery

### Limited evidence to support postnatal antiviral treatment

Among antiviral-treated pregnant women with HBV infection, alanine aminotransferase (ALT) flares can

occur during pregnancy (10.9%), although most occur in the postpartum period (45.7%), as demonstrated by a prospective study of 303 Chinese pregnant women.<sup>54</sup> After cessation of prophylactic antivirals, the HBV DNA level rebounded in nearly all of the women, but only 73% of the women developed ALT flares and 21% of the women required retreatment.<sup>55</sup>

In a study of 91 highly viraemic HBV-infected mothers, the incidences of postpartum flares were similar regardless of whether antivirals were stopped at 2 weeks (50%,  $n=22/44$ ) or 12 weeks (40%,  $n=17/43$ ) after delivery. Additionally, there were no significant differences between the two groups in terms of the timing of flare onset (8.2 vs 10.2 weeks), peak ALT level (229 U/L vs 209 U/L), proportion of severe flares (ie, ALT rise  $\geq 20$  times the upper limit of normal of 19 U/L) [14% vs 12%], and rate of spontaneous resolution of ALT flares (75% vs 53%).<sup>56</sup> Another multicentre study showed that the rates of postpartum ALT flares were similar between women who stopped treatment at delivery (33%,  $n=3/9$ ) and those who continued treatment for a longer duration (22%,  $n=4/18$ ).<sup>57</sup>

Overall, there is no evidence that prolonging the duration of prophylactic antiviral treatment after delivery would reduce the rate or severity of postpartum ALT flares.

### Other international recommendations concerning postnatal antiviral treatment

For HBV-infected pregnant women receiving antiviral prophylaxis during pregnancy solely to prevent MTCT (ie, without maternal indications), the recommended duration of antiviral therapy is not well-defined and varies among guidelines. The European Association for the Study of the Liver guidelines recommend continuing prophylactic antiviral treatment until 12 weeks after delivery.<sup>36</sup> In contrast, the AASLD guidelines recommend stopping prophylactic antiviral treatment at delivery or continuing until 12 weeks postpartum. Notably, the AASLD guidelines are the only international guidelines that emphasise close monitoring of serum ALT every 3 months for up to 6 months after delivery.<sup>35</sup> The Asian Pacific Association for the Study of the Liver guidelines also recommend stopping prophylactic antiviral treatment at delivery or continuing until 12 weeks after delivery (Table).<sup>37</sup>

### Recommendations of the Hong Kong College of Obstetricians and Gynaecologists

The HKCOG recommends the followings:

- Multidisciplinary care is essential to ensure that women are counselled about the existing evidence and allowed to engage in thorough discussion with the treating physician regarding the risks and benefits of the timing for cessation of prophylactic treatment.

- Importantly, although most flares are mild and spontaneously resolve, liver function tests should be performed every 3 months for 6 months after cessation of prophylactic antiviral treatment.<sup>35</sup>
- Hepatitis B virus–infected pregnant women receiving antiviral treatment for maternal indications should continue therapy, even after delivery, and be managed in accordance with standard protocols.<sup>35–37,41</sup>

# Author contributions

All authors contributed to the concept or design, acquisition of data, analysis or interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

# Conflicts of interest

LLY Mak has served as an advisor for Gilead Sciences. Other authors have disclosed no conflicts of interest.

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The guidelines were produced by the Hong Kong College of Obstetricians and Gynaecologists as an educational aid and reference for obstetricians and gynaecologists practising in Hong Kong. These guidelines do not define a standard of care, nor are they intended to dictate an exclusive course of management. They present recognised clinical methods and techniques for practitioners to consider incorporating into their practices. It is understood that clinical management may vary and must always be responsive to the needs of individual patients, as well as the resources and limitations unique to each institution or type of practice. These guidelines also highlight areas of clinical uncertainty in which further research may be warranted.

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