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REVIEW

Prevention of perinatal hepatitis B virus transmission

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Abstract

Purpose Chronic hepatitis B virus (HBV) infection remains endemic and continues to cause significant morbidity and mortality. It is a global health issue and the World Health Organization aims to eradicate HBV by 2030. Since vertical transmission accounts for the majority of chronic HBV infection, pregnancy offers an excellent opportunity to achieve complete HBV eradication by providing effective immunization of the offspring.

Methods We reviewed recent publications identified from PubMed database using a combination of the relevant keywords for HBV, pregnancy, vertical transmission, immunoprophylaxis failure and antiviral treatment.

Results We summarized the evidence of factors associated with, and measures to reduce and prevent maternal to child transmission, including the use of antiviral treatment during pregnancy to prevent immunoprophylaxis failure. Evidence suggested that highly viremia mother can be offered antenatal antiviral treatment to prevent immunoprophylaxis failure. We elaborated the viral load threshold to start maternal antiviral treatment and the importance of timely neonatal vaccination. A clinical algorithm to manage HBV carriers during pregnancy was proposed.

Conclusion Eradication of HBV is achievable with optimal management of HBV carriers, especially during pregnancy by interruption of vertical transmission. Routine antenatal screening and neonatal immunoprophylaxis remain the key measures to reduce the global HBV burden, and additional antenatal antiviral treatment could further minimize the chance of persistent infection in newborns.

Keywords Antiviral treatment · Hepatitis B virus · Immunoprophylaxis failure · Labour · Pregnancy · Vaccination · Vertical transmission

Introduction

Viral hepatitis is the seventh leading cause of death worldwide. According to the World Health Organization (WHO) and Global Burden of Disease study, there has been an increasing trend of mortality from viral hepatitis with 1.34 million deaths in 2015, which is comparable to the mortality from tuberculosis and higher than that from human immunodeficiency virus (HIV) and malaria infection [1, 2]. Hepatitis B virus (HBV) infection remains the commonest form of chronic hepatitis worldwide with an estimated prevalence of 3.5%, which is highest in the Africa (6.1%) and Western Pacific regions (6.2%) [1]. Data from WHO reveal that approximately 257 million people are living with HBV infection, 887,000 people died due to HBV in 2015 and 20–30% of chronic adult carriers would develop HBV complication such as cirrhosis or liver cancer [3]. It is a WHO goal to achieve 90% reduction in incidence and 65% in mortality from the 2015 baseline by 2030, through five interventions, including prevention of vertical transmission and increasing the coverage of third dose HBV vaccination in infancy [4].

Pregnancy offers an excellent opportunity to begin HBV eradication. The risk of acquiring chronic HBV infection is greatest in the perinatal period, with up to 90% of infected newborns becoming chronic carriers [5]. Infected infants become a reservoir for horizontal transmission of HBV infection in the community, as well as for future vertical transmission to the offspring of female carriers and perpetuates a vicious cycle. In this regard, the successful implementation of a universal newborn immunization program has led to a significant reduction in maternal HBV carrier rate by

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interrupting vertical transmission [6]. As HBV carriers are often asymptomatic, universal antenatal HBV screening enables identification of HBV carriers [7], who are unaware of their HBV status, for subsequent disease monitoring, treatment which could also eliminate vertical transmission [4], and the use of passive–active immunization for their infants. Reiteration of the compliance and importance of disease monitoring and treatment are equally important to known HBV carriers who do not receive regular surveillance. Optimal management of HBV carriers during pregnancy fulfills the WHO strategy to control the HBV endemic—to prevent, to test and to treat [1]. We reviewed recent publications identified from PubMed database using a combination of the relevant keywords for HBV, pregnancy, vertical transmission, immunoprophylaxis failure and antiviral treatment. In this review, we discuss the effect of pregnancy on HBV activity and factors associated with maternal-to-child transmission (MTCT). We also suggest an algorithm for the minimization of MTCT.

Hepatitis B virus and pregnancy interaction

In the setting of a successful pregnancy, immune modulation occurs to avoid rejection of the fetal allograft. Maternal regulatory T cells suppress Th1 response and induce Th2 immunity, which leads to an impaired immune reaction towards HBV and facilitates viral activity thus enhancing MTCT [8]. As well, the immature fetal immune system is exposed to maternal hepatitis B e antigen (HBeAg) transferred through the placenta in hepatitis B surface antigen (HBsAg) seropositive mothers, which could induce fetal T cell tolerance to both HBeAg and hepatitis B core antigen (HBcAg) due to the high cross reactivity between HBeAg and HBcAg in terms of T helper cell recognition [9]. Increased regulatory T cells and dysfunctional CD8 T cell found in newborns with HBsAg and HBV DNA detected at birth suggest the development of immune-tolerant HBV infection in the fetus [10, 11]. These may account for persistent HBV infection after birth but the exact mechanism remains unclear.

Effect of pregnancy to hepatitis B virus

The hormonal changes and the altered host immune response may affect HBV activity during pregnancy (Fig. 1). A study in an unselected group of 246 asymptomatic HBV carriers identified at antenatal screening showed that HBV DNA was detected in 48% at the first assessment before 16 weeks' gestation, increasing to 59% at 34–36 weeks and 61% at 6 weeks postpartum [12]. Furthermore, the level of HBV DNA tends to increase in the course of pregnancy, with a mean of 0.4$\log_{10}$ up to $\geq$ 2$\log_{10}$ IU/ml in 5.2% to 10–13%

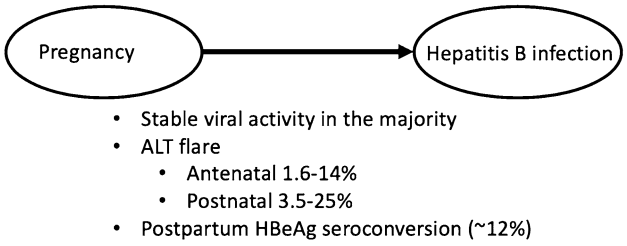

Fig. 1 Effect of pregnancy to hepatitis B infection

[13–15]. However, other studies found no significant HBV DNA change [16] or similar HBV DNA level between trimesters and after delivery [17]. It is likely that the majority of HBV carriers have stable viral activity during and after pregnancy, but increased activity may be found in 5–13% [15–17].

There is risk of alanine aminotransferase (ALT) flare in untreated HBV carriers, in 1.6–14% in the antenatal period with the highest risk during the first trimester [14, 15, 17–19], and 3.5–25% postpartum usually within the first three postnatal months [14, 15, 17–19]. The wide range of incidence probably reflects the lack of standardized consensus on the definition of flare and depends on the intensity and duration of monitoring. Unrecognized peripartum HBV reactivation can lead to maternal death [20].

HBeAg seroconversion denotes the transition of immune active phase to inactive carrier phase and is associated with clinical remission. Compared with the non-pregnant state, pregnancy increases spontaneous HBeAg seroconversion from 2.2 to 14.3% ($p = 0.002$) [21] and 12.5% (5/40) seroconversion at 1 year postpartum [22]. Immune reactivation after delivery could lead to an inflammatory process with ALT elevation and HBeAg seroconversion.

Factors associated with MTCT and immunoprophylaxis failure

HBV is commonly transmitted from carrier mothers to their newborns during pregnancy and through contact with infectious maternal blood/ secretion during delivery [23]. The likelihood of chronic infection in the newborns depends on the maternal HBeAg status, which is around 10–30% in HBeAg(−) carriers and substantially increases to 90% if HBeAg(+) [24, 25]. Hepatitis B immunoglobulin (HBIG) administered to newborn infants at birth has been shown to reduce the risk of vertical transmission from 21 to 6% in HBeAg(+) carriers and 2.6% to 1% in HBeAg(−) carriers in one study [26]. In a cohort of 160 Chinese children born to HBV carrier mothers with timely combined passive–active immunization at birth, only one (0.6%) was found with HBsAg at the age of 18–24 months [27]. Figure 2

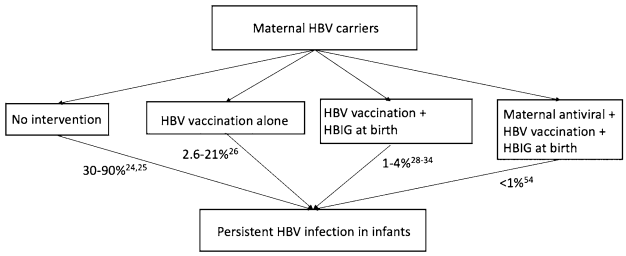

Fig. 2 Possible strategies to prevent HBV vertical transmission

summarizes the possible strategies to prevent HBV vertical transmission. Immunoprophylaxis failure (IF) refers to persistent HBV infection in the newborn despite HBV immunization. IF occurs in around 1–4% of HBV carriers [28–34]. Studies in China showed that the independent factors associated with IF in infants and children include high maternal HBV DNA loads $\geq$ 8 $\log_{10}$ IU/mL, delayed vaccination and inadequate initial injections [35, 36], and having household contacts with HBV carriers and lack of vaccination were risk factors for HBV infection in children aged 1–14 years [37]. Hence, the most important factors in IF are maternal viral load [29, 30, 34, 38] and timing of the birth dose vaccination [35]. Other possible factors include germline infection at the time of conception, prenatal invasive procedures, and placental infection (Fig. 3) [38]. In a systematic review of 28 studies, caesarean delivery was associated with risk reduction in HBV vertical transmission (RR 0.51 95% CI 0.44–0.60, $p < 0.001$) [39]. However, the use of prenatal maternal HBIG vaccinations could affect the result by offering protective effect in some women. There was heterogeneity in antenatal maternal HBIG administration, definition of vertical transmission (some studies defined vertical transmission before completion of vaccination) and postnatal HBIG vaccination to infants among studies. No information on maternal HBV DNA was available. In a recent prospective observation study, the risk of IF was not associated with prolonged rupture of membranes, labour and mode of delivery even in women with high viral load after neonatal HBV immunization [40]. The purported protective role of caesarean delivery could not be demonstrated due to the HBIG administration [39]. A number of studies have reported varying effects of antenatal administration of HBIG from 28 weeks gestation onwards to prevent MTCT. However, a Cochrane analysis with 36 studies found a very low quality of evidence to recommend prenatal maternal HBIG use to reduce vertical transmission [41]. Therefore, the role of caesarean delivery and maternal HBIG during pregnancy to prevent MTCT and decrease IF remains questionable when prenatal antiviral treatment to carriers and timely postnatal HBV immunization to infants can be provided routinely. Finally, horizontal transmission can occur in infancy before the infant could develop a sufficient anti-HBs response after vaccination [42] and mutant in 'a' determinant region results in an immune escape [43].

Various authorities including the American Association for the Study of Liver Diseases (AASLD), the Asian Pacific Association for the Study of the Liver (APASL) and the European Association for the Study of Liver (EASL) have published recommendations regarding the third trimester use of antiviral treatment in highly viremic mother (Table 1) [44–46]. Antiviral therapy should be considered in women with high viral load to reduce the risk of IF. AASLD and EASL recommended a conservative cutoff of 5.3 $\log_{10}$ IU/ml and APASL suggested 6–7 $\log_{10}$ IU/ml. The difference in the recommended viral load threshold could be due to the significant heterogeneity in the rate of prenatal invasive

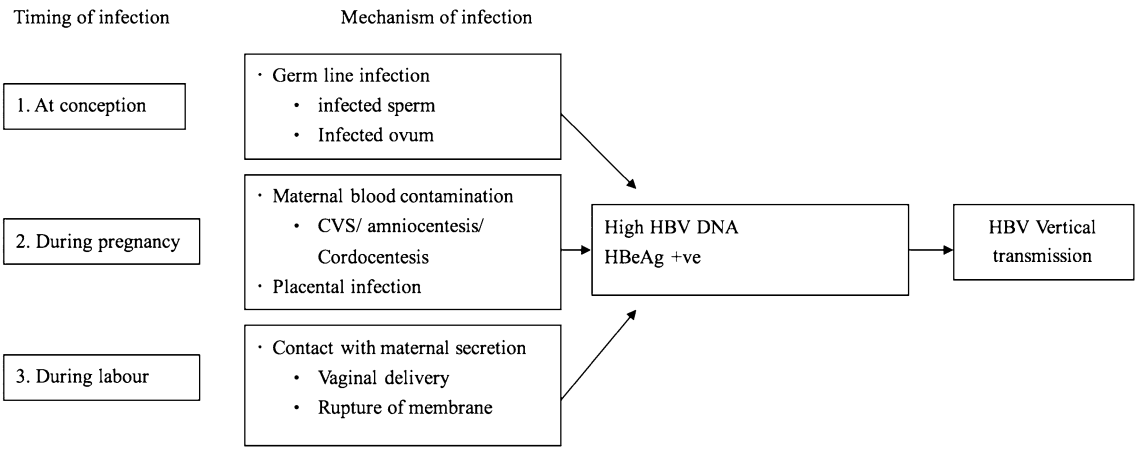

Fig. 3 Possible mechanisms of in-utero and perinatal hepatitis B virus transmission. Adapted with permission from Elsevier. Cheung et al. Towards complete eradication of hepatitis B infection from perinatal transmission: review of the mechanisms of in-utero infection and the use of antiviral treatment during pregnancy. Eur J Obstet Gynecol Reprod Biol. 2013;169:17–23

Table 1 Recommendation from guidelines to start antiviral treatment in prevention of immunoprophylaxis failure

	Viral load to consider antiviral treatment	Gestational age to begin antiviral treatment (weeks)	Antiviral treatment	Mode of delivery	Antiviral treatment after delivery	Breastfeeding
AASLD	> 200,000 IU/mL	28–32	Tenofovir	Caesarean section is not indicated	Could stop after delivery or up to 4 weeks postpartum	Not contraindicated in women on antiviral treatment
EASL	> 200,000 IU/ml	24–28	Tenofovir	Not mentioned	Continue up to 12 weeks after delivery	Not contraindicated in women on Tenofovir
APASL	> 6–7 $\log_{10}$ IU/ml, or in lower DNA levels after discussion	28–32	Tenofovir or Telbuvidine	Not mentioned	Could stop after delivery for breastfeeding	Not encouraged during antiviral treatment

AASLD American Association for the Study of Liver Diseases, *EASL* European Association for the Study of Liver, *APASL* Asian Pacific Association for the Study of the Liver

test, HBV DNA quantification platform, prenatal HBIG intervention, timing of birth dose vaccination and use of neonatal HBIG in observational cohort studies evaluating IF rate with respect to the maternal HBV DNA [28–33]. These factors could influence the viral load cutoff to predict IF. For example, the rate of IF would be increased in highly viremic mother received amniocentesis [47] and in infants with delayed birth dose vaccination [35]. A prospective cohort with maternal HBV DNA quantification at 28–30 weeks examined the risk of IF in 641 pregnancies with timely vaccination and description of prenatal invasive tests. The risks of IF of maternal HBV DNA level of < 7.2, 7.2–8.2, > 8.2 $\log_{10}$ IU/ml were 0%, 8.6%, and 3.1%, respectively [34]. It seems that a higher viral load threshold may be used in units where neonates could receive timely birth dose [42, 48].

Antiviral treatment

Similar to HIV and genital herpes [49, 50], antiviral treatment during pregnancy has been recommended to decrease the risk of vertical transmission of HBV. The antiviral therapy is usually started in highly viremic women between 28–32 gestational weeks to allow adequate treatment duration to bring down the viral load at delivery, assuming that the delivery occurs at term.

Lamivudine and telbivudine: efficacy and safety

Brown et al. [51] carried out a systematic review of 26 studies with 3622 HBV carriers to assess the efficacy of antiviral treatment in prevention of IF. Eleven and nine studies compared lamivudine and telbivudine with control group, respectively, and two other studies compared lamivudine with telbivudine. Lamivudine and telbivudine significantly reduce the maternal HBV DNA before delivery (lamivudine RR 57.1, 95% CI 3.5–921.4, telbivudine RR 52.8, 95% CI 10.7–261.8) and at 4–8 weeks postpartum (lamivudine RR 70.9, 95% CI 8.5–590, telbivudine RR 102, 95% CI 14.4–722.8). Telbivudine was associated with a greater viral load suppression at delivery than lamivudine (RR 1.8, 95% CI 1.3–2.6), but there was no difference in the infants' HBsAg(+) rate at 6–12 months. Both significantly reduced the infants' HBsAg(+) rate at 6–12 months by 11.7% (RR 0.3, 95% CI 0.2–0.6) and 15.8% (RR = 0.2, 95% CI 0.1–0.5), respectively.

The Antiretroviral Pregnancy Registry is an international registry to allow prospective voluntary report of possible teratogenicity from antiviral use during pregnancy. Only lamivudine and tenofovir had sufficient cases for birth defect analysis [52]. The risk of birth defect from lamivudine was comparable to the risk in general population (first trimester use 3.1%, second/ third trimester use 2.7%). Systematic review also found that the use of lamivudine or telbivudine was not associated with increased risk of congenital malformation and other maternal or neonatal complications (postpartum haemorrhage, caesarean delivery, elevated creatine kinase, preterm birth and lower Apgar scores) [51].

Tenofovir disoproxil fumarate (TDF): efficacy and safety

TDF becomes the treatment of choice during pregnancy in view of its potent effect and the higher resistance barrier [53]. It is also effective in pregnant women who developed lamivudine or telbivudine resistance [54]. Pan et al. [55] conducted an open-label randomized controlled trial in 200

HBeAg(+) HBV carriers with viral load > 200,000 IU/ml. TDF was started in 100 HBV carriers from 30–32 to 4 weeks postpartum. After a median of 8.6 weeks treatment, 32% and 98% of the treatment and control group had HBV DNA > 200,000 IU/ml at delivery, respectively ($p < 0.001$). All infants received standard HBIG and HBV vaccination. The risk of IF at 7 months was significant lower in the treatment group in per protocol analysis (0% vs 7%, $p = 0.01$). A systematic review of ten studies with 733 HBV carriers evaluated the efficacy of maternal TDF use in HBV carriers [53]. TDF significantly reduced the maternal HBV DNA level (OR 260.41, 95% CI 29.92–2266.17, $p < 0.00001$) and newborn HBV DNA positivity at birth (OR 0.16, 95% CI 0.07–0.39, $p < 0.0001$), compared with control group. IF rate was also significantly lower after TDF treatment (OR 0.20, 95% CI 0.09–0.46, $p = 0.0002$). However, a double-blinded randomized placebo controlled trial carried out by Jourdain et al. [42] did not demonstrate a beneficial effect from TDF in HBeAg(+) HBV carriers with a median baseline HBV DNA of 8 $\log_{10}$ IU/ml. In this study, 322 HBeAg(+) HBV carriers were randomized to receive either TDF or placebo from 28 gestational weeks to 8 weeks after delivery. A significant drop of 2.6 $\log_{10}$ IU/ml in HBV DNA at delivery was noted in TDF group after a median of 10.7 weeks treatment, compared with no change in the placebo group ($p < 0.001$). At delivery, 12% and 90% HBV carriers had HBV DNA > 200,000 IU/ml in the treatment and placebo group, respectively. All infants received routine HBIG and HBV vaccination. IF at 6 months was comparable in both groups (0% in treatment group vs 2% in placebo group, $p = 0.12$). Centers for Disease Control and prevention recommended that serologic testing of infants after vaccination should not be performed before 9 months of age [56]. Detection of IF at 6 months may, therefore, miss some IF due to prolonged incubation period following passive immunization. Inclusion of women with low viral load may include women who are not at risk of IF [57]. These could account for the negative findings.

Maternal creatine kinase elevation was noted with TDF; however, most cases were asymptomatic [53, 55]. Side effects from TDF were grade 1 or 2 without significant maternal morbidities and usually subsided with symptomatic treatment or temporary TDF cessation. The rate of caesarean delivery, postpartum haemorrhage and preterm delivery was not affected by TDF [53]. The data from Antiretroviral Pregnancy Registry showed that the risk of birth defect was similar to the background risk (2.4% and 2.0% if earliest exposure occurred in the first and second/third trimester, respectively) [52]. A systematic review also did not identify any obvious teratogenicity effect or congenital anomaly related to maternal TDF use [53]. There was concern about the effect on bone mineral density and infants' growth [58] but this was not observed in a prospective longitudinal study, which showed no association between the duration of in-utero TDF and early linear growth up to 48 weeks in 464 infants [59, 60]. Maternal TDF use is generally not a contraindication for breastfeeding due to the limited amount of TDF in breast milk [44, 46]. There is risk of postpartum flare after TDF treatment withdrawal, but usually mild and asymptomatic [42, 55]. It has been shown that antiretroviral therapy can be associated with mitochondrial disease in the offspring, and in the case of TDF, nephrotoxicity with distinctive clinical, pathological, and mitochondrial abnormalities has been documented in HIV-infected adult patients [61]. Hence, it remains unknown if there could be a long-term renal damage in the offspring of HBV carrier mothers treated with TDF during pregnancy.

In summary, data from research setting suggested highly viremia mother can be offered antenatal antiviral treatment to prevent IF. Optimal implementation would depend on the health care system infrastructure and could be particularly difficult in resource-limited countries due to economic and logistic constraints [62]. Women should be reassured about the lack of teratogenic effect; however, long-term evaluation on the offspring and the unknown effect on the immune response of vaccination following in-utero antiviral exposure are lacking and should require further study.

Clinical approach to hepatitis B carriers in pregnancy

Figure 4 summarizes the suggested approach to HBV carriers in pregnancy. In the first trimester, baseline liver function test and HBV DNA quantification should be performed to guide the necessity in initiating antiviral treatment for maternal indication or prevention of IF. They should be reassured that most of them usually cope well during pregnancy without significant adverse pregnancy outcomes. There is the issue of erroneous diagnosis without early pregnancy assessment, mistaking exacerbations during pregnancy as one of the obstetric complications such as hyperemesis gravidarum, pre-eclampsia, haemolysis elevated liver enzyme and low platelet (HELLP) syndrome, and acute fatty liver of pregnancy. Multidisciplinary approach involving hepatologist/gastroenterologist and obstetricians during pregnancy is crucial to facilitate detailed explanation on the rationale of antiviral treatment, if indicated, and at the same time reassuring its safety. Moreover, it could integrate the HBV carriers for subsequent disease surveillance and treatment after delivery. For women who conceive while putting on lamivudine, telbivudine or TDF, they could consider to continue the antiviral treatment with its safety profile in early pregnancy use [52, 63–66]. For women who use other antiviral medication, switching to TDF should be considered. Monitoring of liver function and HBV DNA should be done for women who opt

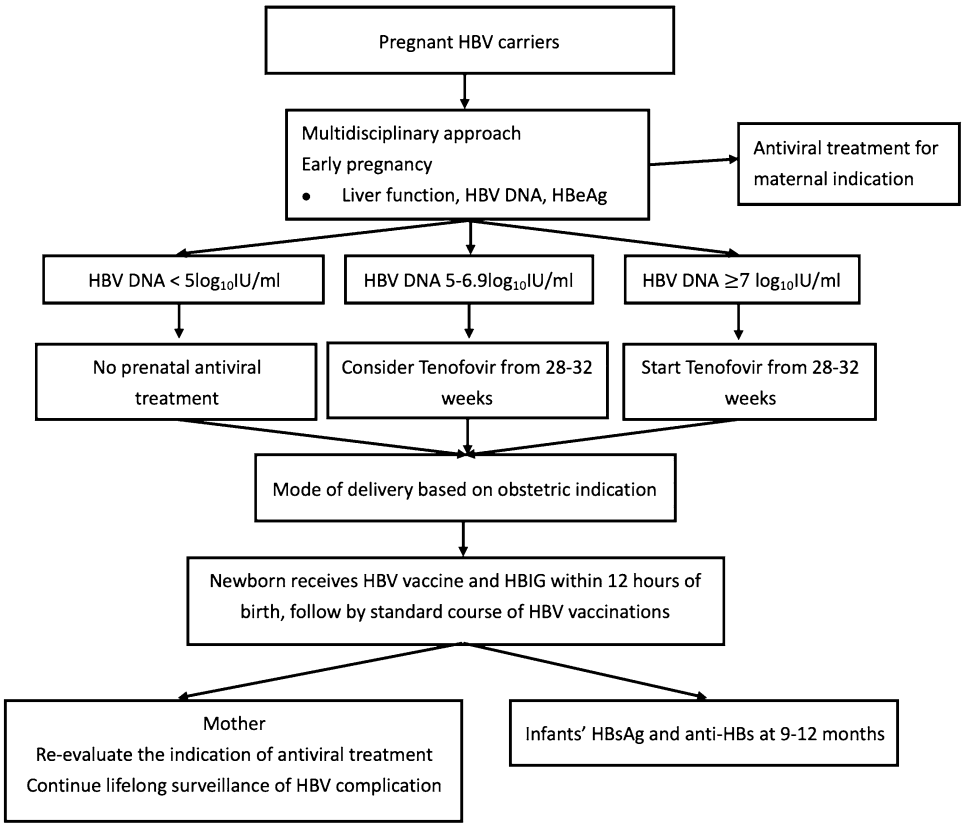

Fig. 4 Suggested clinical management to HBV carriers in pregnancy

to stop the antiviral treatment during pregnancy for possible ALT/HBV DNA flare.

Where antiviral treatment is indicated, TDF should be the drug of choice during pregnancy in view of its potent effect, and the possibility of pre-existing or emergent-resistant mutant from prior lamivudine and telbivudine treatment. HBV DNA is a better predictor and should be used to guide management. HBeAg(+) and HBsAg level should not be an indicator to start antiviral treatment during pregnancy for prevention of IF. The use of TDF and telbivudine in HBeAg(+) carriers (with no viral load restriction on inclusion criteria) did not show significant effect in IF reduction, when compared to control group [42, 67]. The potential mitochondrial disease and renal damage in the offspring should not be disregarded until evidence on the long-term safety of TDF on the offspring becomes available.

The ideal timing and the appropriate cutoff to initiate antiviral treatment remain controversial. Although theoretical concern exists for early in-utero infection, unable to cover prenatal invasive procedure in second trimester, and inadequate viral load suppression at delivery if antiviral treatment is begun in early third trimester, maternal antiviral treatment starting from 28 weeks appears to offer adequate protection to infants. Therefore, the current evidence suggests that TDF could be started since early third trimester of pregnancy to prevent IF.

Since higher risk of IF has been consistently demonstrated in women with viral load ≥ 7 $\log_{10}$ IU/ml, antiviral treatment is therefore recommended to decrease IF in this group. For maternal viral load between 5–7 $\log_{10}$ IU/ml, it remains debatable whether antiviral treatment should be given for IF prevention. In the randomized controlled trial, no IF was detected if the HBIG and HBV vaccines were given at a median 1.3 h and 1.2 h after birth, in HBeAg(+) women with a higher viral load (median HBV DNA at 8 $\log_{10}$ IU/ml, ~ 90% > 200,000 IU/ml) [42]. We suggest an individualized management with emphasis on the timely birth dose in this group, and antiviral treatment may be an option if delayed birth dose is anticipated. Women with HBV DNA < 5 $\log_{10}$ IU/ml could be reassured with the negligible risk of IF and prenatal antiviral therapy is not needed.

Caesarean delivery is not indicated to decrease IF and breastfeeding should not be contraindicated. After delivery, timely HBV vaccination and HBIG should be given to the newborn as soon as possible and within 12 h after delivery [1]. Women should be followed up for postpartum flare during the first 3 months after delivery, which is usually mild and asymptomatic. The need of postpartum antiviral treatment should be reviewed. The infant should be examined at 9–12 months for HBsAg and HBV immunity [56].

Conclusion

Eradication of HBV is achievable with optimal management of HBV carriers, especially during pregnancy by interruption of vertical transmission. Routine antenatal screening and neonatal immunoprophylaxis remain the key measures to reduce the global HBV burden, and additional antenatal antiviral treatment could further minimize the chance of persistent infection in newborns. Long-term follow-up of the offspring is currently lacking and would be essential to demonstrate the long-term safety of in-utero antiviral treatment. Well-designed studies are required to define the best timing and viral load threshold to initiate antiviral treatment.

Author contributions KWC, MTYS and TTHL: project development, manuscript writing.

Compliance with ethical standards

Conflict of interest All authors have no conflicts of interest to declare.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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