Antiviral Therapy for Chronic Hepatitis B in Pregnancy

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Semin Liver Dis 2013;33:138–146.

Abstract

The management of chronic hepatitis B (CHB) during pregnancy remains a challenge and involves various aspects of maternal–fetal care. Despite the standard immunoprophylaxis, a significant portion of infants born to highly viremic mothers remain infected with hepatitis B virus (HBV). Emerging data suggest that antiviral therapy in the third trimester can prevent immunoprophylaxis failure. To minimize fetal exposure to antiviral agents, antiviral therapy during pregnancy should be reserved for mothers with advanced disease or who are at risk for hepatic decompensation. Current safety data suggest that lamivudine, telbivudine, or tenofovir may be used during pregnancy. However, the timing in initiating antiviral therapy requires careful assessment of risks and benefit. The authors provide a systematic review of the features of HBV during pregnancy, risk factors for vertical transmission, and evidence-based data on antiviral use during pregnancy. They propose an algorithm to assess the need of antiviral treatment and monitor mothers with CHB.

Keywords
- vertical transmission
- hepatitis B in pregnancy
- fetal exposure
- antiviral treatment
- drug safety

It is estimated that two billion people worldwide have been infected with hepatitis B virus (HBV) with more than 350 million with chronic infection.[1] Those with chronic hepatitis B (CHB) have up to a 15 to 40% risk of developing cirrhosis and hepatocellular carcinoma in their lifetime. In Africa and Asia, 8 to 10% of the adult population is chronically infected with HBV, most having been infected during childhood. Up to 50% of new cases of HBV infection are due to vertical transmission.[2] In countries of low endemicity defined by HBV surface antigen (HBsAg) prevalence $< 2\%$, such as the United States and northern or western Europe, the majority of new infections occur among adolescents and adults. These infections are attributable to high-risk sexual activity and injection-drug-use exposures.[3] However, with immigration of individuals from high-risk geographic areas into areas of low risk, prevalence of HBV infection is expected to increase in low prevalence countries, particularly among certain foreign-born groups.

Current indications for the treatment of CHB are based on the disease stage determined by HBV DNA level, serologic status, and evidence of liver injury.[4,5] Most patients receive treatment because they are in the immune-active phase, have advanced fibrosis/cirrhosis, or have multiple risk factors for liver cancer.[4–6] The current therapeutic armamentarium for CHB involves oral nucleos(t)ide analogues and pegylated interferon (PEG IFN). Only tenofovir (TDF) and entecavir (ETV) are recommended as first-line oral antiviral therapies. Lamivudine (LAM) and telbivudine (LdT), despite their safety profiles, have high rates of resistance that can result in cross resistance with other oral therapies. Adefovir (ADF) has only moderate antiviral activity with increased rates of resistance and nephrotoxicity with long-term use.

Issue Theme Current Perspectives on Chronic Hepatitis B; Guest Editors, Stephen Locarnini, MD, PhD, FRC(Path), and Alexander Thompson, MD, PhD, FRACP

DOI http://dx.doi.org/10.1055/s-0033-1345718.
ISSN 0272-8087.

The management of CHB during pregnancy remains a challenge with unique issues that involve various aspects of care for both the mother and fetus. Special considerations include the effect of HBV on maternal and fetal health, effects of pregnancy on the course of HBV infection, antiviral treatment during pregnancy for maternal liver disease, and the prevention of perinatal transmission. Here we provide a systematic review on these issues with a focus on the safety and potential benefit of antiviral therapy during pregnancy.

Maternal and Fetal–Neonatal Outcomes

The impact of CHB on pregnancy outcomes has not been clearly defined. Most published data have suggested that CHB negatively impacts maternal outcomes. Possible associations have been described between CHB and gestational diabetes mellitus,[7–9] antepartum hemorrhage,[9] increased risk of prematurity,[10] and lower birth weight.[11] A retrospective study by Lao et al reported that a significantly higher prevalence of gestational diabetes mellitus was found in mothers with HBsAg positivity ($n = 1138$) when compared with those ($n = 12{,}547$) without CHB.[7] In a case-control retrospective study by Tse et al, HBsAg positive mothers ($n = 253$) were compared with HBsAg negative mothers ($n = 253$), matched by age, parity, and year of delivery. They observed that maternal HBsAg positivity was associated with increased antepartum hemorrhage, gestational diabetes, and threatened preterm labor.[9]

Data are conflicting regarding fetal outcomes from maternal CHB infection. Recent studies suggest that maternal CHB infection was associated with preterm labor, perinatal mortality, congenital malformations, and low birth weight.[10,11] Conversely, one large retrospective study compared 824 HBsAg-positive mothers to 6281 HBsAg-negative controls. No differences were seen in gestational age at delivery, birth weight, neonatal jaundice, congenital anomalies, incidence of prematurity, or perinatal mortality.[12] Other studies have shown that the strength of these associations is still unclear.[13,14] A significant adverse neonatal outcome is the development of fulminant hepatitis in some newborns when HBV is transmitted from HBeAg-negative mothers.[15] The impact of CHB on the infant's outcome is further discussed in the Mother-to-Child Transmission of HBV section.

Effect of Pregnancy on CHB Infection

Women with CHB infection generally do well during pregnancy. Pregnancy is a hormone-induced immune-tolerant state and is associated with high levels of adrenal corticosteroids with modulation of cytokines in the immune response. Studies have shown that although no significant difference was seen in viral levels during pregnancy, alanine aminotransferase (ALT) had a tendency to increase late in pregnancy and postpartum.[16,17] With the expected but sudden decrease in levels of corticosteroids during the postpartum period, this may create a setting comparable to the acute withdrawal of steroids that can result in hepatitis flares.[18–20] As a result, mild elevation in ALT levels is not uncommon and usually well tolerated, but severe flares (ALT $> 5 \times$ baseline value or $10\times$ upper limit of normal [ULN]) can occur during the first few months after delivery.[18,19] Some studies have shown that postpartum flares can lead to HBV e antigen (HBeAg) seroconversion ranging from 12 to 17%.[20] Severe exacerbation of the disease leading to decompensation has been reported, but is very rare.[21] Ter Borg et al reported that the administration of lamivudine during third trimester did not prevent flares.[19] However, factors such as maternal age, parity, and precore or basal-core promoter mutations do not appear to be associated with postpartum HBeAg clearance.[20,22] There is limited understanding of the natural history of HBV during pregnancy. Thus, mothers with CHB should be monitored closely for hepatitis flare and exacerbation during the postpartum period.

Mother-to-Child Transmission of HBV

The implementation of universal maternal screening programs and passive–active immunoprophylaxis of infants has reduced mother-to-child transmission (MTCT) rates to 5 to 10%. However, up to 30% of infants born to highly viremic mothers may fail immunoprophylaxis.[23] Recent studies demonstrated that the serum level of maternal HBV DNA is an independent risk factor for immunoprophylaxis failure.[24–26] Although Xu et al suggested that maternal HBeAg positivity was an independent risk factor for immunoprophylaxis failure,[25] this finding has not been confirmed by others. In addition, mothers who are HBeAg-negative, but with a high level of HBV DNA, have shown increased risk in HBV transmission to the infant during birth.[27] Wiseman et al evaluated 138 babies born to HBsAg-positive mothers.[26] Forty-seven women in the study were HBeAg-positive with viral levels > 8 $\log_{10}$ copies/mL, and 9% (4 of 47) of their infants failed immunoprophylaxis in a 9-month follow-up, compared with none of the infants when maternal HBV DNA was ≤ 8 $\log_{10}$ copies/mL; however, these findings were based only on a few cases with immunoprophylaxis failure. Transmission risk with maternal HBV DNA levels between 6 to 8 $\log_{10}$ copies/mL may not have been noted in the aforementioned studies.

A recent large-scale study evaluating 1,043 mother–infant pairs by Zou et al demonstrated that there was a linear correlation between immunoprophylaxis failure rates and maternal HBV DNA levels.[24] Among 869 infants given appropriate immunoprophylaxis with serologic testing at age 7 to 12 months, 27 (3.1%) infants had immunoprophylaxis failure. When maternal predelivery HBV DNA levels were stratified to < 6 $\log_{10}$ copies/mL, 6 to 6.99 $\log_{10}$ copies/mL, 7 to 7.99 $\log_{10}$ copies/mL, and ≥ 8 $\log_{10}$ copies/mL, the corresponding rates of immunoprophylaxis failure were 0%, 3.2% (3 of 95), 6.7% (19 of 282), and 7.6% (5 of 66), respectively ($p < 0.001$ for the trend). The study suggested that maternal HBV DNA levels > 6 $\log_{10}$ copies/mL reduced prophylaxis effective rate (PER). In a recently published expert consensus from the First International Symposium on Hepatitis B Infection in Special Populations,[28] it is recommended that pregnant women with HBV DNA > 6 $\log_{10}$ copies/mL ($> 200{,}000$ IU/mL) at the third

trimester be considered for antiviral prophylaxis for prevention of MTCT.

Concerns of Antiviral Therapy during Pregnancy

Limited Efficacy on Maternal Disease with Short-Term Therapy

Most pregnant women with significant viremia have well-compensated disease. As per current standard of care, patients in the immune-tolerance phase should be monitored without treatment.[4,5] However, they may receive antiviral therapy for the prevention of MTCT at the third trimester or rarely, for the management of maternal disease due to CHB activation in pregnancy.[4,28] Current available data on antiviral therapy during pregnancy are largely from trials evaluating antiviral-therapy use in the prevention of MTCT.

A recent study of 135 pregnant women who received LdT starting either at the second (101 of 135) or third trimester (34 of 135) demonstrated a > 3 $\log_{10}$ copies/mL HBV DNA reduction, and 33% had HBV DNA < 500 copies/mL at the time of delivery.[29] Eighty-eight mothers who discontinued LdT treatment at 1-month postpartum had a rise in serum HBV DNA levels 4 weeks later with levels returning to baseline prior to the initiation of LdT. None of the treated patients had sustainable viral suppression. At the time of delivery, 83% (30 of 36) of patients who had baseline elevation of ALT prior to pregnancy had normalization of their ALT. The ALT remained within normal limits during treatment. Eighteen of 88 mothers who discontinued LdT at 1 month postpartum had fluctuation in ALT levels, but only one had ALT $> 5\times$ ULN. However, 13% of 38 mothers who continued on LdT treatment up to postpartum week 110 had HBeAg seroconversion. Similar results were observed by Pan et al on 88 mothers with active CHB who had elevated ALT and HBV DNA > 6 $\log_{10}$ copies/mL.[30] Maternal HBsAg loss did not occur in either trial.

Xu et al reported that mothers treated with LAM at the third trimester had HBV DNA reduction from baseline of 2,220 ($\pm$ 1,610.9) mEq/mL to 41.7 ($\pm$ 177.4) mEq/mL at week 4 of therapy and remained suppressed throughout the treatment period.[23] However, HBV DNA levels returned to baseline in all patients after treatment cessation at week 4 postpartum. For mothers with elevated ALT levels at baseline, the median level in the LAM-treated group decreased to $< 1\times$ ULN by week 4 of treatment and remained within the range of $1.2\times$ ULN during the trial. The above trials showed limited efficacy on maternal disease because LdT and LAM treatment were discontinued within a few weeks postpartum.[23,29,30] In addition, more than 70% of patients enrolled were immune tolerant. Treatment end points for this phase of CHB infection remain poorly defined by current standard of care.

Safety Concerns on Fetal Exposure to Antiviral

The development of the embryo is at its most critical stage during the first trimester. It is during organogenesis between weeks 4 to 14 of gestation that exposure to teratogenic drugs could result in birth defects. In 1979, the U.S. Food and Drug Administration (FDA) implemented labeling requirements and each drug is classified into one of five categories based on the safety data for pregnancy (►**Table 1**). All HBV antiviral drugs are category C, except for tenofovir and telbivudine, which are category B drugs. However, this system may oversimplify the clinical complexities that exist when evaluating the risks to the fetus and the benefits of treating maternal disease. In May 2008, the FDA announced that the five-category system would be replaced by a narrative framework consisting of three sections with one section on clinical consideration of addressing risk assessment after exposure.[31] Currently, this new system has not yet been implemented.

Table 1 FDA pregnancy categories and HBV antiviral therapy

Category	FDA description	HBV therapy
A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).	
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women or animal studies, which have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.	Telbivudine Tenofovir
C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.	Lamivudine Entecavir Adefovir
D	There is positive evidence of human fetal risk based on adverse-reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.	
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse-reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.	Interferon

Abbreviations: FDA, U.S. Food and Drug Administration; HBV, hepatitis B virus.

Table 2 Antiviral pregnancy registry data on antiviral therapy

Drug	FDA pregnancy category data	1st trimester birth defects/ live births (%)	2nd/ 3rd trimester birth defects/ live births (%)
Lamivudine	C	127/4088 (3.1%)	186/6635 (2.8%)
Tenofovir	B	31/1370 (2.3%)	18/782 (2.3%)
Telbivudine	B	0/9	0/9
Entecavir	C	1/42	0/2
Adefovir	C	0/48	0/0
PEG IFN α-2A/ IFN α-2B	C	N/A	N/A

Source: Antiviral Pregnancy Registry Interim Report (January 1, 1989–January 31, 2012), issued in June 2012.[32]
Abbreviations: FDA, U.S. Food and Drug Administration; PEG IFN, pegylated interferon; N/A, not applicable.

Established in 1989, the Antiretroviral Pregnancy Registry (APR) has been evaluating the teratogenic effects of human immunodeficiency virus (HIV) agents.[32] APR data confirmed that birth defect rates from LAM or TDF exposure were comparable to those seen in the general population (►**Table 2**). The limitations of the APR include underreporting, lack of long-term follow-up of infants, and lack of confirmation of actual diagnosis of birth defects. In addition, there are no data on fetal miscarriages or infant developmental delays that may have occurred later.

Among CHB pregnant mothers enrolled in prospective trials, fetal abnormalities were extremely low. Xu et al reported one infant (1 of 89) born to a LAM-treated mother with atrial septum defect, Ebstein anomaly, and pneumothorax.[23] Similar outcomes were observed in prospective trials on mothers treated with LdT.[23,29,30] In a recent large prospective trial collecting "real-world" data with enrollment of 700 mothers into treatment arms for LdT or LAM versus no treatment,[33] only 0.97% infants had birth defects in the treatment group compared with 1.7% in the untreated group ($p > 0.05$). It is worth noting that all the above trials provided follow-up on infants with a maximum period of 52 weeks.[23,29,30,33] Long-term safety data remain unavailable. Other adverse events that have been reported with nucleos(t)ide analogues use include mitochondrial damage, lactic acidosis, and acute fatty liver. Although rare, lactic acidosis is a serious and potentially fatal complication leading to fetal death even if the mother is able to recover. The development of fatal lactic acidosis has only been reported in infants who had exposure to HIV antiviral drugs. However, this has not been observed in infants born to mothers on antiviral treatment for HBV.[34,35]

Based on a recent study from the Medical Research Council (MRC) clinical trials unit in the United Kingdom, TDF use during pregnancy did not increase risk for kidney disease, birth defects, or growth abnormalities in infants born to HIV-infected women in Africa.[36] The majority of mothers were taking TDF-containing regimens for HIV before and throughout pregnancy. Among 226 live births, there was no increase in the proportion of infants who died shortly after birth (3%) or who had birth defects (3%). The surviving infants were HIV-negative and had normal growth without renal problems or bone fractures up to age 4. Similar findings on fetal exposure to TDF were reported by other studies including 81 infants observed by Vigano et al[37] and 2,029 infants observed by Siberry et al with 1-year follow-up.[38] Currently, under the Pediatric Research Equity Act (PREA), an ongoing controlled trial is evaluating renal function and bone loss in pediatric HBV-infected patients.

Antiviral Therapy for the Reduction of Immunoprophylaxis Failure

Current immunoprophylaxis is less efficacious in mothers with high serum levels of HBV DNA > 6 $\log_{10}$ copies/mL or 200,000 IU/mL.[24,29,33,39] However, there is growing evidence that treatment with LAM, LdT, or TDF during the third trimester may reduce the risk of transmission by lowering maternal viremia prior to delivery.[23,29,33,39,40] There is very limited data on other antiviral treatments for mothers with HBV. They will not be discussed in this review.

Treatment with Lamivudine

In a recent randomized, placebo-controlled, double-blinded study evaluating 115 HBeAg-positive mothers who had HBV DNA $\geq$ 1,000 mEq/mL ($\sim$ 8 $\log_{10}$ IU/mL),[23] mothers were randomized to receive LAM (150 mg/d) or placebo starting at 32 weeks of gestation with treatment cessation at 4 weeks postpartum. Of infants born to mothers who were treated with lamivudine, 18% (10 of 56) were HBsAg-positive at 52 weeks compared with 39% (25 of 59) infants in the control group with statistical significance in the intention to treat analysis. However, there was no difference on MTCT rates between the treated and placebo group in the sensitivity analysis. LAM treatment was well tolerated without safety concerns. It should be noted that results may also have been affected by a high number of infants who were lost to follow up, particularly in the control group. A recent study observed that LAM use in the second or third trimester of pregnancy has similar efficacy in preventing MTCT in highly viremic mothers.[39] Thus, LAM treatment may be deferred until the third trimester for high-risk mothers to minimize fetal exposure and the development of LAM resistance in the mother.

Treatment with Telbivudine

In a recent study evaluating the efficacy of LdT in preventing MTCT, LdT (600 mg/d) was administered at the gestational age of 20 to 32 weeks in women with HBV DNA > 7 $\log_{10}$ copies/mL.[29] The baseline characteristics of mothers in the LdT-treated group ($n = 137$) and untreated group ($n = 97$) were comparable. All infants received appropriate immunoprophylaxis. At age 7 months, none of the infants in the treatment group had positive HBsAg or detectable HBV DNA. In contrast, 8% ($p < 0.01$) of infants in the control group (7 of 88) were HBsAg-positive along with detectable HBV DNA. There was no significant difference in fetal development or infant outcomes between the two groups in terms of body weight, height, or Apgar score. Another recent large-scale, real-world study evaluated highly viremic mothers who had third-trimester treatment with LdT ($n = 252$) or LAM ($n = 51$) versus no treatment ($n = 345$).[33] Immunoprophylaxis failure rates in their paired infants were 1.9%, 3.7% versus 7.6%, respectively (all treated vs. untreated = 2.2% vs. 7.6%, $p = 0.0023$). The above trials were nonrandomized studies with only short-term follow-up. Despite these limitations, these studies tend to support the use of LdT to reduce MTCT in highly viremic mothers.

Treatment with Tenofovir

Although TDF has been used in HIV or HIV/ HBV coinfected mothers, little data exist for mothers with HBV monoinfection. A recent case series study evaluated HBeAg-positive mothers with HBV DNA > 7 $\log_{10}$ copies/mL who received TDF 300 mg/d at the third trimester.[40] All infants received hepatitis B immune globulin (HBIG) and the three-series vaccination. A significant reduction in serum HBV DNA was achieved at delivery compared with baseline (mean 5.25 ± 1.79 vs. 8.87 ± 0.45 $\log_{10}$ copies/mL, respectively; $p < 0.01$). The 11 infants born from mothers who received TDF had no obstetric complications or birth defects. All infants were HBsAg-negative at 28 to 36 weeks after birth. A large prospective randomized control trial studying the prevention of HBV MTCT with the use of TDF in the third trimester is currently being conducted in Asia with anticipated trial results available in 2014.[41]

Resistance and Hepatitis Flare from Antiviral Therapy

Current available data have shown that antiviral resistance to LAM or LdT therapy in treatment naïve pregnant mothers are very uncommon due to the short duration (8–12 wk) of therapy at the third trimester of pregnancy.[23,29,33,40] For treatment-experienced patients when indicated, initiating TDF is recommended because of its favorable resistance profile and high potency in viral suppression. Per the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases,[4,5] it is considered one of the first-line therapies in standard treatment. In addition, switching treatment to TDF is effective in mothers with nucleoside resistance.[6,42] Another concern is antiviral therapy inducing hepatitis flare, which can occur during treatment or after cessation of treatment postpartum. Xu et al reported that when LAM was initiated at the third trimester,[23] ALT elevations occurred in 25% (22 of 89) of mothers compared with 49% (30 of 61) in the placebo group. After treatment cessation at week 4 postpartum, ALT elevation occurred in 19% (16 of 83) of mothers in the LAM group compared with 33% (15 of 46) in the placebo group. Only one subject in each group had ALT $> 10\times$ ULN following treatment cessation. In a study evaluating 38 CHB mothers either HBeAg-positive or HBeAg-negative who received LAM during the third trimester, postpartum flares (ALT $> 3\times$ ULN) were seen in 62% of LAM treated mothers after treatment cessation, compared with 42% of untreated mothers.[19]

Antiviral Therapy for the Management of Maternal Disease

When pregnant women experience an acute hepatitis flare or have preexisting severe or advanced liver disease such as cirrhosis, antiviral therapy may be initiated during pregnancy or continued if antiviral drug has been started prior to pregnancy.[4,42] The potential safety concerns of fetal exposure to antiviral agents should not preclude the initiation of therapy, which may be potentially lifesaving for both mother and fetus. Recent studies have described pregnancy as causing progression of underlying liver disease with a variable presentation ranging from mild hepatitis flare to acute hepatic decompensation.[16,18] For pregnant mothers who have acute hepatitis flare (ALT $> 10\times$ ULN or $5\times$ baseline values) with or without hepatic decompensation, TDF treatment is preferred and should be continued throughout the pregnancy. Experience in nonpregnant patients with acute exacerbation of CHB suggested that TDF treatment also reduced short-term mortality rates when acute on chronic liver failure developed.[43]

It is important to identify mothers with cirrhosis who have high risk for maternal and perinatal complications. In a recent retrospective study evaluating 399 cirrhotic mothers from 1993 to 2005,[44] 15% of women in the cirrhotic group had hepatic decompensation during pregnancy. Maternal and fetal mortality were higher in the cirrhosis group compared with the control group, 1.8% versus 0% ($p < 0.0001$) and 5.2% versus 2.1% ($p < 0.001$), respectively. Therefore, it is advised that antiviral therapy be initiated during pregnancy for cirrhotic mothers (or continued in cirrhotic patients who are already on treatment).[4] Maternal complications such as gestational hypertension, placental abruption, and peripartum hemorrhage were increased in the group with cirrhosis when compared with age-matched controls. Higher rates of prematurity and growth restriction were seen in the infants born to mothers with cirrhosis. Thus, close monitoring is necessary in addition to antiviral treatment.

Discussion and Strategies

With our understanding of the current safety data on HBV antiviral therapy, there should be a thorough discussion on indications for antiviral treatment and timing of the initiation of treatment for women with CHB who are contemplating pregnancy. For patients who are already on treatment, the decision to withhold or continue therapy at the time of

conception should also be discussed thoroughly based on the detailed evaluation of the disease stage and liver histology if available.

Women with Active CHB

It is recommended that patients in the immune clearance or reactivation phase be placed on antiviral treatment as per standard of care.[4,5] It appears to be more beneficial if the HBV DNA can be reduced to undetectable level before conceiving, particularly as Nie et al observed that a significant percentage of mothers with HBV viremia had HBV replication in oocytes and in the embryo.[45] For treatment naïve patients who are planning future pregnancy, it may be worth considering a finite duration of treatment with PEG IFN to control HBV viremia with the potential goal of achieving HBeAg loss or seroconversion prior to pregnancy. Efforts should be made to prevent pregnancy during IFN therapy and a 6-month washout period after treatment discontinuation. If pregnancy planning is not feasible, first-line oral antiviral is preferred to manage maternal disease and suppress viremia. At the time of conception, antiviral treatment could be withheld in patients without acute exacerbation of hepatitis or advanced liver disease. A recent study has demonstrated that there were no significant adverse events in these mothers who discontinued treatment.[22] In the event of severe hepatitis flare (ALT $>$ 10$\times$ ULN or 5$\times$ baseline) or the need to suppress high-level viremia at the third trimester for the prevention of MTCT, reinitiation of treatment may be indicated. For mothers with cirrhosis or advanced histology, antiviral therapy should be continued throughout pregnancy to prevent disease progression and decompensation. The drug of choice is TDF, but LdT may be used in countries where TDF is unavailable. Close surveillance for antiviral resistance is mandated after the use of LdT for $>$ 12 weeks.[29]

Women in the Immune-Tolerance Phase

Women in the immune-tolerance phase who are contemplating having children should be monitored closely after conception. Antiviral treatment may be offered at the beginning of the third trimester for the following conditions[28]: (1) maternal HBV-DNA level $\geq$ 6 $\log_{10}$ copies/mL during the late second trimester, (2) history of a child with previous immunoprophylaxis failure, and (3) preterm labor. Monotherapy with LAM, LdT, or TDF is an acceptable option and treatment can be discontinued at week 4 postpartum or earlier if breastfeeding is desired. Close monitoring at 4- to 6-week intervals of viral levels and liver enzymes for potential off-treatment flare within 12 weeks of treatment cessation is recommended. If a severe hepatitis flare occurs (or evidence of immune-clearance phase) during pregnancy, TDF is recommended as first-line treatment and should be continued through pregnancy because long-term treatment is anticipated.

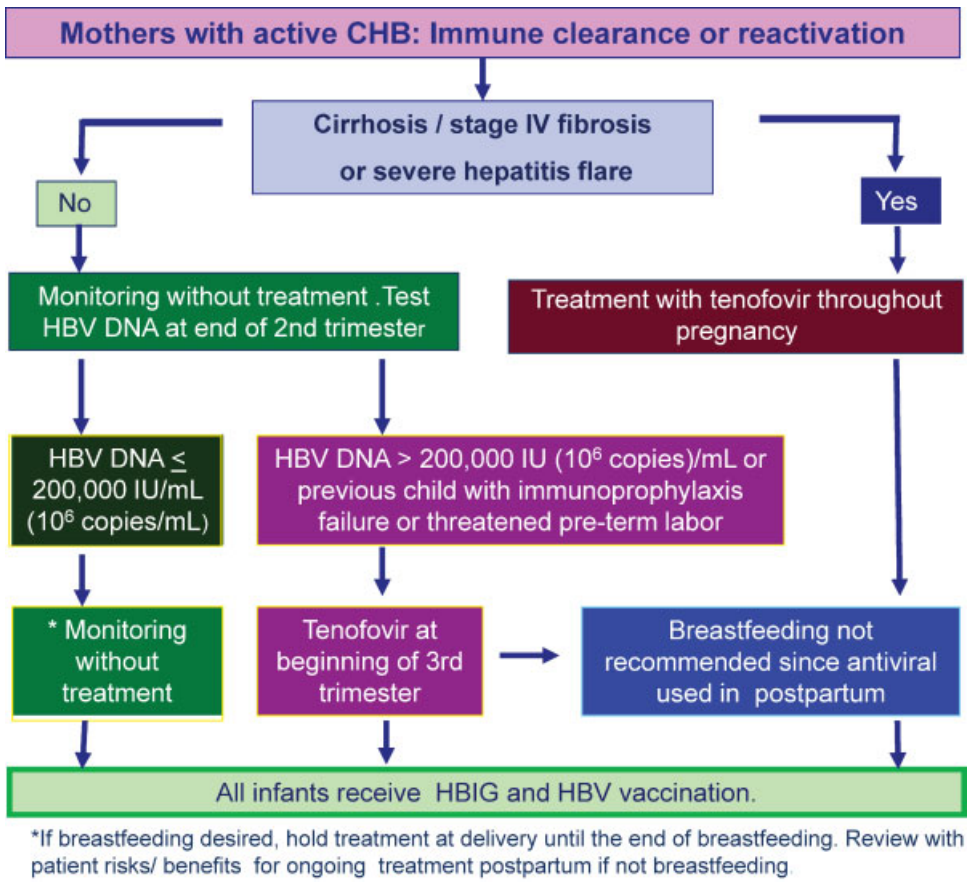

Fig. 1 Assessment of antiviral therapy in mothers with active disease or at risk for hepatic decompensation. CHB, chronic hepatitis B; HBIG, hepatitis B immune globulin; HBV, hepatitis B virus.

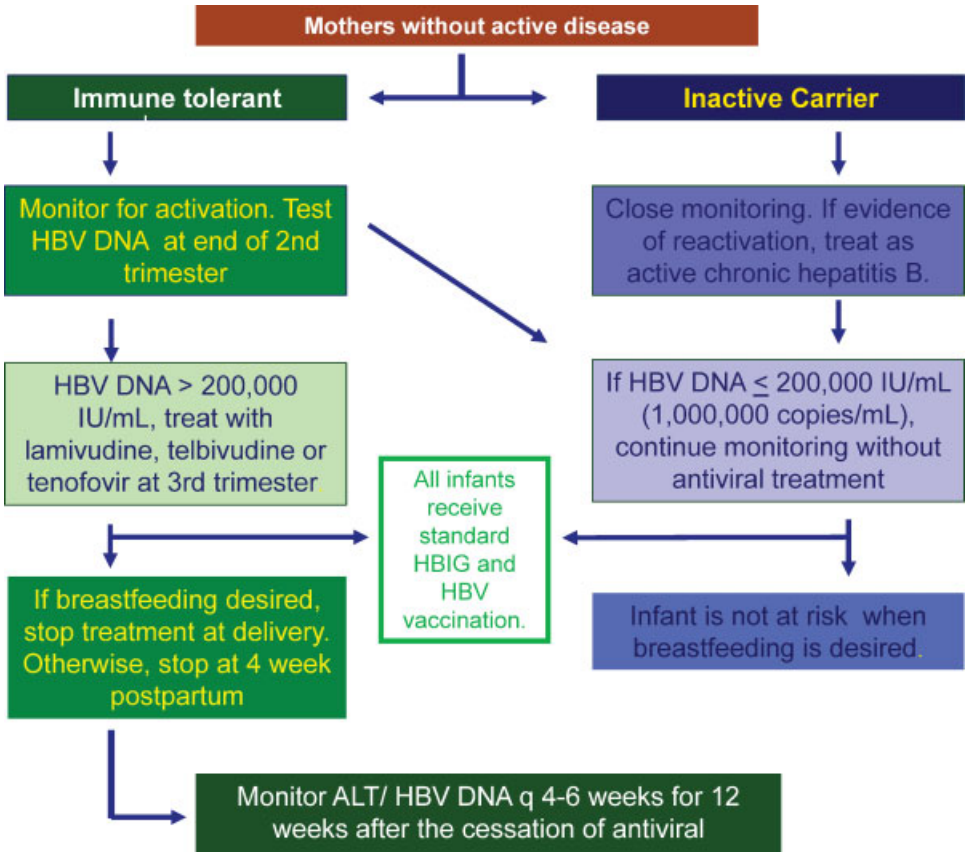

Fig. 2 Assessment of antiviral therapy and monitoring in mothers at the phase of immune tolerance or inactive carrier. ALT, alanine aminotransferase; HBIG, hepatitis B immune globulin; HBV, hepatitis B virus.

Antiviral Therapy in Mothers Anticipating Breastfeeding

Although HBsAg can be detected in breast milk,[46] breastfeeding has not been shown to increase the risk of transmission compared with bottle feeding. A study evaluating 147 infants born to HBV-carrier mothers showed no association between breastfeeding and the development of CHB infection in the infants.[47,48] Neonates who are correctly immunized may be breastfed.[4,5] Breastfeeding can be started as long as the infant has received HBIG and the first dose of vaccination at birth. For mothers who remain on antiviral therapy postpartum, breastfeeding has generally not been recommended.[5] Not much is known regarding the extent of drug exposure to the infant during breastfeeding as nucleoside/nucleotide analogues are excreted into the breast milk. A study by Van et al[49] showed that breast milk contained lower levels of TDF compared with maternal blood in mothers taking TDF. The study suggested that there was unlikely any biological effects in the nursing infant. However, the drug safety for infants has not been established.

Summary

Antiviral therapy in pregnant women remains a challenge and requires an individualized and detailed assessment of the risks of drug exposure to the fetus weighed against the benefits of treatment. The benefits include reducing MTCT of HBV in highly viremic mothers and managing maternal disease due to acute exacerbation of CHB or progression of advanced fibrosis/cirrhosis. With our understanding of the current safety data and benefits of HBV antiviral therapy, we propose an algorithm to evaluate pregnant women for antiviral therapy, which is shown in ►**Figs. 1** and **2**. At present, more data are needed regarding the long-term safety of fetal exposure to antiviral therapy. In addition, the efficacy and safety of tenofovir in the management of pregnant mothers with CHB requires further investigation. Lastly, the use of antiviral therapy to prevent MTCT in highly viremic mothers in conjunction with infant immunoprophylaxis deserves further exploration and will require universal implementation because the success of such interventions may contribute significantly in achieving the ultimate goal of global eradication of HBV.

Acknowledgments

We would like to acknowledge Dr. Geneve Allison and Dr. Sonali Paul for their assistance in proofreading.

Disclosure

For the past 5 years, Dr. Calvin Q. Pan has received research grants from Gilead, Bristol Myers Squibb, Novartis, and Roche. He also serves as a consultant, advisor, and speaker for Gilead and Bristol Myers Squibb.

For the past 5 years, Dr. Hannah M. Lee has received research grants from Gilead and Bristol Myers Squibb. She has also served as a consultant and advisor for Gilead.

Author Contribution

Both authors participated in the outline discussion and development on the first draft. Dr. Pan further revised the draft, verified citations, and performed critical review. Dr. Lee provided editorial work and proofreading.

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