A Review of Antiviral Use for the Treatment of Chronic Hepatitis B Virus Infection in Pregnant Women

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Abstract: Mother-to-child transmission (MTCT) of hepatitis B virus (HBV) remains high even with the proper use of active-passive immunoprophylaxis in newborns. Mothers with significant viremia are at a much higher risk of MTCT; therefore, treatments aimed at lowering HBV DNA levels during pregnancy may ultimately decrease global disease burden. The exact threshold for treatment remains controversial; however, most studies have accepted levels greater than 2×5 $\log_{10}$ IU/mL as significant viremia. We reviewed the most recent literature on antiviral efficacy, maternal and fetal safety, and viral resistance patterns when used for short-duration therapy in pregnancy. The literature review shows that antiviral therapy during pregnancy significantly reduces maternal HBV DNA levels with subsequent reductions in infant HBV infections. Tenofovir disoproxil fumarate (TDF) is associated with mild gastrointestinal distress and may cause decreased fetal bone growth (although long-term studies are needed to evaluate the clinical significance of this finding), and the impact of this drug is likely limited when use is restricted to the third trimester. Lamivudine and telbivudine remain inferior to TDF in regard to resistance profiles. Overall, TDF, lamivudine, and telbivudine in conjunction with standard immunoprophylaxis are recommended for use in pregnant women with significant HBV viremia ($>2 \times 5$ $\log_{10}$ IU/mL) to prevent MTCT and appear reassuring in regard to their maternal and fetal safety profiles.

Keywords
Hepatitis B virus, pregnancy, antiviral efficacy, antiviral safety

Hepatitis B virus (HBV) infects up to 2 billion people worldwide,[1] with as many as 248 million going on to develop chronic HBV infection. Of those 248 million people, up to 648,000 will die of life-threatening complications such as hepatic decompensation, cirrhosis, and/or hepatocellular carcinoma, making HBV the tenth leading cause of death worldwide.[1-5]

The most common route of HBV acquisition in underdeveloped areas remains mother-to-child-transmission (MTCT),[5,6] with prior studies showing that even in low-endemic regions, up to one-third of chronic HBV infections may be attributable to perinatal transmission.[7,8] Increased maternal HBV viral load and hepatitis B e antigen (HBeAg) positivity at the time of pregnancy have been shown to increase the likelihood of transmission to the newborn.[5,9] Without any prophylaxis, mothers with active replication, as measured with HBeAg positivity, have up to a 90% chance of transmitting the virus to their infant.[10,11] Of patients infected in infancy, 90% will go on to develop chronic infections as compared to 50% of those infected at an age younger than 3 years and 5% or less of those infected in adulthood.[5] HBV infection ultimately leads to an increased risk of fibrosis leading to cirrhosis as well as hepatocellular carcinoma.[12,13] Once a patient is infected, antiviral drugs can reduce the severity of complications; however, eradication or viral cure of HBV, usually defined as loss of hepatitis B surface antigen (HBsAg) and development of hepatitis B surface antibodies (HBsAb), is rare.[14] Therefore, prevention of transmission remains the most effective way of reducing overall global disease burden.

Current recommendations from the World Health Organization and Centers for Disease Control and Prevention on the prevention of MTCT of HBV include both passive and active immunoprophylaxis to the newborn using hepatitis B immune globulin and HBV vaccination. However, 10% to 30%[3,15] of infants develop HBV infection when mothers have significant viremia (defined as HBV DNA >2 × 5 $\log_{10}$ IU/mL).[5,16,17] Given the significant rates of preventable transmission in this group, there is a need to elucidate the safety and efficacy of antiviral drugs in pregnancy in order to minimize the risk of HBV transmission to the fetus.

One of the largest studies on the safety of antiviral drugs in pregnancy was published in 2012 and looked at data from the Antiretroviral Pregnancy Registry (APR), in which 13,711 cases were analyzed.[18] In regard to chronic HBV medications, only tenofovir disoproxil fumarate (TDF) and lamivudine had sufficient exposure data (>200 enrolled cases) to detect significant increases in birth defects. The vast majority of cases were patients with HIV infection, with only a small percentage including patients being treated for HBV monoinfection. However, this study found that the prevalence of birth defects for all antiviral drugs was statistically similar to the prevalence reported in the general population (2.8% vs 2.7%). Additionally, the birth defect prevalences for lamivudine- and TDF-containing regimens were similar to those of other classes of antiretroviral drugs (lamivudine, 3.1%; TDF, 2.4%; all antiretroviral drugs, 3.0%). The study also found no difference in birth defect rates based on time of exposure in utero (first and second vs third trimester exposure) to these medications, supporting the lack of teratogenicity.[18]

Since the publication of APR findings in 2012, multiple studies have looked further into this topic. This review article focuses on the most recent literature regarding updates in efficacy, maternal and fetal safety profiles, and viral resistance patterns with the use of the antiviral medications TDF, telbivudine (Tyzeka, Novartis), lamivudine, adefovir dipivoxil, and entecavir during pregnancy. The goal of this article is to increase awareness of this topic and present options to medical providers to prevent MTCT of HBV.

Methods

Eligibility Criteria

All studies included in the literature review were controlled or comparative studies that enrolled pregnant women with chronic HBV infection. Studies that enrolled infants who did not receive immunization during the first week postpartum were excluded. Abstracts and individual articles were reviewed and chosen if they contained recent clinical information (within the last 7 years) regarding use of antiviral drugs in pregnancy and looked at outcomes including MTCT, maternal and fetal safety, antiviral efficacy, and/or viral resistance patterns.

Search Strategy

We searched PubMed on July 20, 2016 and reviewed all of the recent literature using controlled vocabulary with high-yield keywords to search for any studies regarding antiviral use for chronic HBV in pregnancy.

Additional Data

The most recent interim report from the APR was also reviewed, which included data from January 1, 1989 to January 1, 2016.

Results

Our initial search resulted in 303 articles. Of those, 23 were chosen for review based on quality, relevance to the topic of interest, and date of publication. There were 2 randomized, controlled trials; 12 nonrandomized, controlled trials; and 9 meta-analyses or review articles.

Tenofovir Disoproxil Fumarate

TDF remains the first-line therapy for chronic HBV infection during pregnancy based on its safety and resistance profile as well as its potency and efficacy.[3,18,19] It is currently classified as a Pregnancy Category B drug (no

evidence of risk to humans; either animal findings indicate risk but human findings do not, or, if no adequate human studies have been conducted, animal findings are negative).

A recent randomized, placebo-controlled trial by Pan and colleagues evaluated 200 HBeAg-positive mothers with HBV DNA levels greater than 2 × 5 $\log_{10}$ IU/mL, and compared TDF therapy (300 mg daily) from 30 to 32 weeks of gestation to 4 weeks postpartum vs controls.[15] Patients were followed until 28 weeks postpartum. Pan and colleagues found a marked reduction in maternal viral load, with 68% of TDF-treated patients achieving HBV DNA levels less than 2 × 5 $\log_{10}$ IU/mL vs 2% of controls (*P*<.001).[15] The median HBV DNA level at delivery was significantly lower in the TDF group (4.7 $\log_{10}$ IU/mL vs 8.0 $\log_{10}$ IU/mL; *P*<.001). The study also found a reduction in MTCT for TDF compared to control in both the per-protocol and intention-to-treat analyses (0% vs 7%; *P*=.01 and 5% vs 18%; *P*=.007, respectively). For maternal safety, mothers receiving TDF therapy had increased levels of creatine kinase (7% vs 0%; *P*=.006), although these findings were not clinically significant, as all patients were asymptomatic. Additionally, more patients in the TDF group had alanine aminotransferase (ALT) elevations after discontinuing therapy compared to the control group (45% vs 33%; *P*=.03). There was no significant difference in the fetal safety profiles between groups. The study also looked at resistance profiles via direct HBV genome sequencing when virologic breakthrough occurred. Of the 5 women in the TDF group with viral rebound, genome sequencing revealed that all 5 were genotype C wild-type with no mutations.[15]

An opt-in, prospective, multicenter, observational study looked at 120 pregnant women with a high viral load (>7 ± 0.5 $\log_{10}$ IU/mL) and compared TDF-treated and lamivudine-treated patients with controls who did not receive antiviral therapy, beginning at approximately 32 weeks gestation.[20] The TDF group had greater virologic efficacy than the lamivudine group, with a mean reduction of 3.64 $\log_{10}$ IU/mL vs 2.81 $\log_{10}$ IU/mL, respectively (*P*=.01). MTCT for TDF vs lamivudine vs control was 2%, 0%, and 20%, respectively (*P*=.03). For fetal and maternal safety, no significant differences were found in any obstetric or birth outcomes between the groups, including congenital abnormalities and neonatal growth percentiles. TDF was associated with increased gastrointestinal side effects, including nausea and diarrhea in 4 women. Of note, this study contained a small number of controls, as a large percentage was lost to follow-up.[20]

A prospective, multicenter trial of 118 HBsAg- and HBeAg-positive women with HBV DNA levels at least 7.5 $\log_{10}$ IU/mL compared TDF (300 mg daily) given from 30 to 32 weeks gestation through 1 month postpartum to control.[21] At delivery, the HBV DNA levels in the TDF vs control groups were significantly different (4.29 $\log_{10}$ IU/mL vs 8.1 $\log_{10}$ IU/mL; *P*<.001), with 98.39% of the TDF group reaching levels lower than 6.0 $\log_{10}$ IU/mL at delivery vs 1.79% of the control group. Infants in the TDF group had significantly lower levels of HBsAg positivity at 6 months follow-up (1.54% vs 10.71%; *P*=.0481). However, at follow-up, 1 additional infant in the TDF group became HBsAg-positive, and the difference between groups lost statistical significance (*P*=.1423). The mothers in the TDF group had significantly lesser extents of ALT elevations (*P*=.007) and lower mean levels of ALT (*P*=.0117), although 8 women experienced adverse gastrointestinal effects (nausea/diarrhea) that resolved spontaneously. There was no difference in fetal adverse events.[21]

A 2013 systematic review of potential TDF teratogenicity looked at 19 articles, 3 of which reviewed TDF exposure in rhesus macaques and 16 of which reviewed TDF exposure in humans.[22] In the rhesus macaques, 1 study did not impair fetal growth in utero regardless of exposure during the first vs second trimester, whereas another study showed that first trimester exposure was related to length and birth weight reduction, with lower serum insulin-like growth factor 1 (IGF-1) concentrations.[22] In contrast, human infants exposed to TDF had IGF-1 serum concentrations similar to those in control groups. Many articles in the systematic review were reviewed in which TDF was a part of highly active antiretroviral therapy regimens for HIV with no difference in fetal or maternal adverse events. Only 1 study in this review compared TDF to placebo in monoinfected HBV mothers who were HBeAg-positive with HBV DNA levels greater than 6 $\log_{10}$ copies/mL over a 28-month period.[23] Eleven mothers received TDF (300 mg daily) during the third trimester, and compared to the control group, the TDF-treated group had a significant reduction in HBV DNA levels (mean, 5.25 ± 1.79 $\log_{10}$ copies/mL vs 8.87 ± 0.45 $\log_{10}$ copies/mL, respectively; *P*<.01). None of the infants from the TDF-treated group were HBsAg-positive at 36 weeks of age, and none had any congenital defects.[22,23]

In a recent meta-analysis of 26 studies, 4 looked at TDF exposure during pregnancy.[24] The TDF-treated groups had a reduction in infant HBsAg seropositivity by 15.8% (relative risk [RR], 0.2; 95% CI, 0.1-0.7) at 6 to 12 months compared to the control groups. Additionally, there was no difference in congenital malformation rate, prematurity rate, or Apgar scores between groups, although the quality of evidence was moderate to low.

PHACS (Pediatric HIV/AIDS Cohort Study) is a network of 22 clinical sites in the United States and

Puerto Rico that conducted 3 longitudinal cohort studies of children born to HIV-infected mothers.[25] The PHACS SMARTT (Surveillance Monitoring for ART Toxicities) study looked at the association of birth defects in HIV-uninfected infants with different antiretroviral drug exposures in utero.[25] This study found a slightly lower mean length (P=.04) and head circumference (P=.02) at 1 year of age compared to age-matched controls. A study by Siberry and colleagues compared whole-body bone mineral content (BMC) of newborns and found that in utero exposure to TDF resulted in a 12% reduction in total mean whole-body BMC (56.0 g vs 63.8 g; P=.002), which persisted when adjusted for maternal age, smoking, HIV disease status, and infant gestational age, sex, race, and length (P=.013).[26] The DART (Development of Antiretroviral Therapy in Africa) trial looked at in utero exposure of TDF to HIV-positive mothers, and found no evidence of lower birth weights or other growth parameters at up to 4 years of age.[27] Additionally, no other increased congenital or renal abnormalities were associated with TDF exposure.

Data to support TDF use in pregnancy remain the strongest in regard to the drug's resistance profile, with prior studies showing that there is no resistance when used up to 3 years as monotherapy,[28] and less than 1% of resistance or breakthrough viremia even when used up to 6 years as monotherapy.[29,30] A review of resistance profiles from 2013 found that although a rtA194T mutation was found in a study on HIV/HBV-coinfected patients, TDF resistance has yet to be reported in HBV-monoinfected patients, and, in fact, monotherapy with TDF may be as effective as combination therapy.[31]

Telbivudine

Telbivudine is a L-reverse transcriptase inhibitor that has shown to have no effect on human nucleotides and DNA synthesis.[32] It is currently approved by the US Food and Drug Administration for the treatment of chronic HBV, and, along with tenofovir, it is currently classified as a Pregnancy Category B drug. Below is a review of the literature that has been published regarding the safety and efficacy of telbivudine use in pregnancy to prevent MTCT.

In a meta-analysis of 26 articles, 9 articles were reviewed comparing telbivudine to control.[24] These studies showed that telbivudine improved maternal HBV DNA suppression, improved maternal ALT normalization, and increased HBeAg loss at delivery at 4 and 28 weeks postpartum. Telbivudine was found to reduce infant HBsAg seropositivity by 15.8% and infant HBV DNA positivity by 16.2%, with no increase in fetal adverse events.

A pooled analysis published in 2016 reviewed 18 publications including 1739 pregnancy outcomes of women treated with telbivudine.[33] The prevalence of birth defects was 3.6 out of 1000, which was similar to that of nontreated controls (3.0/1000) and lower than the overall prevalence (14.5-60.0/1000). Additionally, the prevalence of spontaneous abortions was not increased (4.2/1000 vs 16.0/1000). There was a marked reduction in the MTCT rate in the telbivudine-treated group at 0.7% vs 11.9% in controls (P<.001). The analysis reviewed preclinical studies as well and found that high doses (up to 37 times higher than those administered to humans) of telbivudine had no peri- or postnatal developmental toxicity or behavioral changes. The pharmacovigilance database was also reviewed in the pooled analysis, with 489 pregnancy cases reported. Six of 249 live birth cases (2.4%) reported congenital defects, which is similar to the general prevalence. Three studies in the analysis reported resistance rates ranging from 1.2% to 6.5%.

A large prospective, controlled trial looked at 229 HBeAg-positive patients with HBV DNA levels greater than 10^7 copies/mL and compared telbivudine (600 mg daily) given from weeks 20 to 32 of gestation to untreated controls.[32] The trial found a marked reduction in HBV DNA levels (>3 $\log_{10}$ copies/mL reduction), decreased HBeAg levels, and increased normalization of ALT levels (83% vs 57%) in the treatment group. Of the telbivudine group, 33% had undetectable viremia (HBV DNA <500 copies/mL) at delivery compared to 0% in the control group. MTCT was markedly lower in the treatment group (0% vs 8%; P=.001), with a higher proportion of infants also having detectable HBsAbs (100% vs 92%). No adverse events were noted in telbivudine-treated mothers or their infants, and no difference in weight, height, or congenital deformities at follow-up visits was noted. Notable in this study is that 2 of 38 patients developed rt204 mutations to telbivudine.

A meta-analysis by Deng and colleagues looked at 2 randomized, controlled trials and 4 nonrandomized, controlled trials comprising 576 patients, 306 of whom received telbivudine treatment.[34] There was a significantly lower rate of HBsAg seropositivity in newborns from the telbivudine-treated group (8.7% vs 27.1%; RR, 0.31; P<.001 at birth and 0.7% vs 12.2%; RR, 0.11; P<.001 at 6-12 months), with a similar finding for HBV DNA–positive rates (2.3% in the treatment group vs 17.2% in the control group; RR, 0.18; P<.001 at birth and 0.9% vs 14.6%; RR, 0.09; P=.0001 at 6-12 months). The frequency of creatine kinase elevation was not significantly different between groups, and maternal HBV DNA levels were markedly lower in the treatment group. The quality and grade of studies reviewed were notably not high.

A prospective, open-label, interventional trial looked at HBeAg-positive mothers with HBV viral load greater than 6 $\log_{10}$ copies/mL.[35] Two hundred fifty-two patients received telbivudine compared to 51 who received lamivudine and 345 controls. Patients treated with telbivudine had a decline greater than 4 $\log_{10}$ copies/mL (mean viral load, 3.16 $\log_{10}$ copies/mL) compared to no change in the control group (P<.001), with 36% of the treatment group reaching a viral load less than 500 copies/mL compared to 0% of the control group (P<.001). No infants in the telbivudine group acquired HBV infection compared to 2.84% in the control group. Rates of ALT elevation in the treatment group were significantly higher (16.0% vs 2.8%; P<.001). There was no difference in fetal adverse events, and there were no cases of viral mutation and resistance.

Another prospective, open-label trial looked at 88 HBeAg-positive pregnant women with HBV DNA levels greater than 6 $\log_{10}$ copies/mL and elevated ALT levels.[36] Fifty-three patients received telbivudine starting in the second or third trimester vs 35 controls. At 28 weeks, there was a significant difference in the telbivudine vs control groups in regard to maternal HBV DNA levels less than 500 copies/mL, normalization of ALT, and HBeAg seroconversion (58% vs 0%, P<.001; 92% vs 71%, P=.008; and 15% vs 0%, P<.001; respectively). No infants in the telbivudine group vs 8.6% in the control group had immunoprophylaxis failure (P=.29). There was no difference between maternal adverse events or infant congenital deformities, gestational age, height, weight, or Apgar scores. Additionally, there was no incidence of virologic breakthrough in the telbivudine group. Notable limitations to this study include use of a single center and its small population size.

One concern regarding telbivudine resistance overall is that only a single site substitution is needed at the YMDD motif (M204I) to induce resistance, which is a lower genetic barrier to resistance compared to TDF or entecavir.[37] An additional concern is that the M204I mutation also reduces susceptibility to other L-nuceloside analogs such as lamivudine or entecavir, which may limit future treatment options.[37]

One study that compared virologic efficacy of telbivudine vs entecavir when used for short durations in patients with HBV-related advanced hepatocellular carcinoma found no episodes of viral resistance when used for 24 weeks.[38] A separate review article on telbivudine found fewer cases of treatment failure and virologic resistance when compared to lamivudine at both 52 and 104 weeks, and only after 2 years was there a significant development of resistance (5.0% vs 25.1% for HBeAg-positive patients).[9] Additionally, there was less resistance in patients who had rapid suppression in viral loads.[9] Thus, although resistance remains more of a concern for telbivudine than newer agents (ie, TDF), when used for a short duration (3 to 4 months) in pregnancy, telbivudine may be a favorable option.

Lamivudine

Lamivudine, a reverse transcriptase inhibitor, is the longest-used antiviral drug for the treatment of chronic HBV and is currently classified in Pregnancy Category C (animal reproduction studies have shown an adverse event on the fetus; no adequate or well-controlled studies in humans).

A meta-analysis and systematic review of 26 studies, 14 of which looked at lamivudine, found that lamivudine improved maternal HBV DNA suppression before delivery and 4 to 8 weeks postpartum, reduced infant HBsAg seropositivity by 11.7% (RR, 0.3; 95% CI, 0.2-0.6), and reduced infant HBV DNA seropositivity by 21.2% (RR, 0.3; 95% CI, 0.2-0.6).[24] There was no difference in lamivudine vs control regarding either maternal or fetal harmful outcomes.

A prospective cohort study by Yu and colleagues looked at 200 women (100 with normal ALT levels and 100 with abnormal ALT levels) who were all HBeAg-positive and had HBV DNA levels equal to or greater than 1.0×10^7 copies/mL.[39] Fifty women in each ALT category cohort received lamivudine (100 mg daily) from 24 to 32 weeks of gestation. In the treatment group, maternal HBV DNA levels declined markedly before delivery compared to the control group. ALT levels in the abnormal liver function test groups normalized equivalently between the treatment and control groups (6.83% vs 8.79%; P>.05). The rates of MTCT between the treatment and control groups were 0% and 7%, respectively (P<.05), with no difference in congenital malformations, birth weight or height, or maternal complications between groups.[39]

A randomized, multicenter, double-blind, placebo-controlled trial by Xu and colleagues looked at 150 mothers with HBV DNA levels greater than 1000 mEq/mL and assigned them to placebo (n=61) vs lamivudine (n=89) from 32 weeks gestation to 4 weeks postpartum.[40] Maternal HBV DNA levels in the lamivudine group decreased to a mean of 51.4 mEq/mL vs 2168.8 mEq/mL in controls, with 13% in the lamivudine group vs 0% in the control group achieving undetectable HBV DNA levels at the time of delivery. For mothers with elevated ALT levels at baseline, those in the treatment group had significantly lower levels both at delivery and postpartum compared to the control group, whose levels reached up to 6 times the upper limit of normal. At 52 weeks follow-up, the incidence of infant HBsAg seropositivity and detectable HBV DNA was 19% and 20% in the treatment group vs 39% and 46% in the control group (P=.014 and P=.003, respectively). Of note, there was a large dropout rate in

this study, with a 13% loss in the treatment group and 31% loss in the control group. Therefore, in the sensitivity analysis, the rate of MTCT was actually 6% for the treatment group vs 12% for the control group (P=.368). The proportion of infants with detectable HBsAbs was higher in the treatment group (84% vs 61%; P=.008). There was no difference in maternal or fetal adverse events in either group, and comparisons in general activity, weight, length, and head circumference were no different at 52 weeks.[40]

A meta-analysis by Shi and colleagues looked at 10 randomized, controlled trials that included 951 HBV-carrier mothers.[41] Newborns in the treatment group had 12.7% to 33.2% lower incidence of MTCT at 9 to 12 months detected by HBsAg (P<.01) and HBV DNA (P<.001). There was no significant increase in adverse events in either mothers or infants at 12 weeks follow-up. Importantly, the studies in this analysis were not of high quality and had evidence of selection and publication bias.[41]

In an open-label, prospective trial of HBeAg-positive mothers with a HBV viral load greater than 6 $\log_{10}$ copies/mL, the lamivudine group had a HBV DNA viral load decline greater than 3 $\log_{10}$ copies/mL (mean viral load, 3.78 $\log_{10}$ copies/mL) compared to the control group (P<.001), with 29% reaching a viral load less than 500 copies/mL compared to 0% of the control group (P<.001).[35] No infants in the lamivudine group were positive for HBsAg compared to 2.84% in the control group. There was no difference in infant safety reports and no cases of viral mutations.

An ongoing concern with lamivudine is its low barrier to resistance, with up to 70% of strains becoming resistant over time.[42] Prior studies have shown that brief treatment in the third trimester can lead to resistance (rtM204I/V and rtA181T mutants) in up to 19% of women.[43]

Adefovir Dipivoxil and Entecavir

There are no current studies available regarding the safety of adefovir dipivoxil or entecavir in pregnancy. Both medications have been added to the APR; however, not enough reported cases to date have been collected to detect a significant difference in adverse events. As a result, neither is currently recommended for use during pregnancy.

Updates in the Antiviral Pregnancy Registry

The International Interim Report for the APR from January 1, 1989 through January 1, 2016 has reviewed 17,899 cases, with 18,206 outcomes and 16,963 live births with exposure to antiviral drugs at any time during pregnancy.[44] This registry continues to analyze approximately 1300 pregnant women in the United States exposed to antiretroviral drugs annually, which accounts for approximately 15% of the HIV-positive women who give birth in a year. Another 200 women from other countries are enrolled annually. The current updated report includes 269 (1.5%) women who are monoinfected with chronic HBV.

The prevalence of birth defects per 100 live births with first trimester exposure is 2.8% (95% CI, 2.5-3.2), which is not different from women exposed during the second or third trimester (2.8/100 live births).[44] Out of 16,963 live births, exposure at any time during pregnancy was associated with 476 birth defects (prevalence of 2.8/100 live births), which is similar to data from the Centers for Disease Control and Prevention's surveillance system[45] (2.72/100 live births) and the Texas Birth Defects Registry[46] (4.17/100 live births).

Based on the updated reports, TDF and lamivudine remain the only 2 chronic HBV drugs that have adequate case reports, although telbivudine, adefovir dipivoxil, and entecavir have been added to the APR. There were defects in 143 of 4589 (3.12%) live births exposed to lamivudine and in 61 of 2779 (2.2%) exposed to TDF. Thus far, 60 cases of entecavir exposure have been reported, with 2 (3.3%) birth defects noted. Forty-eight cases have been reported for adefovir dipivoxil and 18 cases have been reported for telbivudine, with no birth defects in either of those groups thus far.[44]

These general prevalence findings of birth defects for all antiretroviral drugs are consistent with findings from Brown and colleagues, who reported a 3.1% prevalence for lamivudine and 2.4% prevalence for TDF, with an overall prevalence of 2.8%.[18]

Discussion

Given the significant proportion of breakthrough HBV infections despite standard immunoprophylaxis combined with the high percentage of infants infected with HBV who go on to develop chronic HBV with associated complications, consideration of additional therapies to prevent MTCT in highly viremic mothers is critical. The exact threshold to define significant viremia remains controversial. This may be a direct effect of using differing units of measurement (eg, copies/mL) obtained via in-house, nonstandardized, polymerase chain reaction assays and then approximated into IU/mL. However, most studies have used at least 6 $\log_{10}$ copies/mL as a cutoff, which would correlate to 2 × 5 $\log_{10}$ IU/mL.

Maternal and Fetal Efficacy

The majority of studies have shown that TDF, lamivudine, and telbivudine are successful in significantly reducing

maternal viral load as well as MTCT. Certain head-to-head trials of telbivudine vs lamivudine have shown that telbivudine decreases HBV viral load faster and more efficaciously, with higher rates of HBV DNA negativity, ALT normalization, and HBeAg loss and seroconversion in the treatment of chronic HBV.[9,42] The 2-year follow-up for telbivudine vs lamivudine found statistically significant differences in therapeutic response (P<.001), achieving nondetectable viremia (55.6% vs 38.5%; P<.001).[9] Another study found that telbivudine compared to lamivudine had a significantly greater HBV DNA suppression at delivery (RR, 1.8; 95% CI, 1.3-2.6), but no difference in HBeAg loss or seroconversion.[5] A different study found that TDF had approximately 1 log greater decline in HBV DNA levels compared to lamivudine.[20] However, another study showed that compared to lamivudine, telbivudine and TDF showed no significant reduction in infant HBsAg seropositivity at 6 to 12 months.[24] Further head-to-head trials between these antiviral drugs are needed to establish an optimal regimen, although most experts recommend TDF if longer-duration therapy or more than 1 pregnancy is expected. Any of the antiviral drugs is likely acceptable for a single pregnancy and short-duration therapy (3-6 months).

Maternal and Fetal Safety

Studies on TDF have raised questions regarding bone health and growth, and this remains an area that requires further research and long-term data acquisition. The limited findings on this topic remain unclear in regard to their clinical significance. Two studies found significant gastrointestinal side effects with the use of TDF, although the symptoms resolved spontaneously in 1 of the studies.[20,21] Additionally, a study found significantly higher rates of ALT flares with telbivudine treatment, which enforces the need for close serologic monitoring if using this medication.[35] Overall, all 3 antiviral drugs had no significantly increased fetal adverse events or congenital malformations.

Resistance Profiles

In the articles reviewed for this paper, both telbivudine and lamivudine were associated with resistance development even during short periods of antiviral therapy during pregnancy,[32,33,42] whereas no such events were reported with TDF monotherapy, supporting prior literature.

Breastfeeding and Length of Antiviral Drug Use Postpartum

The discussion on the length of postpartum antiviral drug use is an important topic as it relates to prevention of puerperal transmission. It has been proven that HBsAg, HBeAg, and HBV DNA are found in breast milk; however, standard immunoprophylaxis studies have shown no increased risk of transmission.[47] The current recommendations put forth by the Centers for Disease Control and Prevention recommend breastfeeding in patients with chronic HBV.[48]

The recommendation on use of antiviral medication during breastfeeding remains controversial, as little is known about exposure risk and overall safety. The studies that have been performed thus far have shown that the exposure from breastfeeding is markedly lower as compared to in utero exposure.[49] Despite these findings, drug labels still recommend against the use of breastfeeding while on TDF, lamivudine, or telbivudine due to lack of data. However, the World Health Organization recommends the use of both TDF and lamivudine for HIV-infected breastfeeding mothers.[3]

In regard to postpartum HBV flares, studies have shown no difference between the prolonged use of antiviral medications vs immediate cessation in the incidence and resolution of flares.[5,50]

The current recommendations from the European Association for the Study of the Liver state that if antiviral therapy is only given for the prevention of perinatal transmission, it may be discontinued within the first 3 months after delivery (Grade C1 recommendation).[14] The Asian-Pacific Association for the Study of the Liver notes that antiviral drugs could be stopped at birth and when breastfeeding starts if there is no contraindication to stopping them (Grade B2) and that breastfeeding is discouraged during maternal antiviral treatment.[51] However, continuation of antiviral agents for patients with ALT flares detected during the treatment period is recommended.[51] The American Association for the Study of Liver Diseases states that breastfeeding is not contraindicated and that the low level of exposure is unlikely to cause significant toxicity but should be discussed with mothers.[52]

Overall, the decision to continue antiviral therapy postpartum should be made on an individual basis. In general, studies have suggested that the decision to stop antiviral therapy should not be made because of concern for prevention of HBV flare or concern for HBV transmission with breastfeeding. Therefore, if the only indication for antiviral therapy is the prevention of MTCT, antiviral therapy may be discontinued shortly after birth. Future studies are needed on this topic.

Conclusion

TDF (Pregnancy Category B), telbivudine (Pregnancy Category B), and lamivudine (Pregnancy Category C) remain adequate treatment options for the prevention of HBV transmission during pregnancy. Decisions regarding

Table. Current Guidelines for the Management of Chronic HBV Infection During Pregnancy

American Association for the Study of Liver Diseases[51]	Antiviral therapy is suggested to reduce the risk of perinatal transmission of HBV in HBsAg-positive pregnant women with HBV DNA levels >200,000 IU/mL. **Quality/Certainty of Evidence: Low** **Strength of Recommendation: Conditional** The use of antiviral therapy is not recommended to reduce the risk of perinatal transmission of HBV in HBsAg-positive pregnant women with HBV DNA levels ≤200,000 IU/mL. **Quality/Certainty of Evidence: Low** **Strength of Recommendation: Strong**
World Health Organization[3]	In HBV-monoinfected pregnant women, the indications for treatment are the same as for other adults, and TDF is recommended. No recommendation was made on the routine use of antiviral therapy to prevent mother-to-child HBV transmission as a result of the current limited and low-quality evidence base.
European Association for the Study of the Liver[14]	Telbivudine, lamivudine, or TDF (as a potent FDA Pregnancy Category B agent) may be used for the prevention of perinatal and intrauterine HBV transmission in the last trimester of pregnancy in HBsAg-positive women with high levels of viremia (serum HBV DNA >6-7 $\log_{10}$ IU/mL). **Evidence Grade: B1**
Asian-Pacific Association for the Study of the Liver[51]	In pregnant women with chronic HBV infection who need antiviral therapy, TDF is the drug of choice for mothers indicated for antiviral treatment during the first through third trimesters of pregnancy. TDF is a Pregnancy Category B drug with adequate safety data in HIV-positive women and has the least chance of viral resistance. **Evidence Grade: B1** For the reduction of risk of mother-to-child transmission that occurs during the perinatal period, the use of short-term maternal nucleo(s)tide analogues starting from 28 to 32 weeks of gestation is recommended using either TDF or telbivudine for those mothers with HBV DNA levels >6-7 $\log_{10}$ IU/mL. **Evidence Grade: B2** Breastfeeding is discouraged during maternal nucleo(s)tide analogue treatment. For those with alanine aminotransferase flares detected during the treatment period, continuation of antiviral treatment according to maternal liver disease status may be indicated. **Evidence Grade: B2**

FDA, US Food and Drug Administration; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; TDF, tenofovir disoproxil fumarate.

which antiviral drugs are the most efficacious need to be balanced against possible maternal and fetal side effects, as well as concern for potential amplification of resistant variants that may affect future treatment options. The current literature is lacking in sufficient high-quality studies with adequate follow-up time; therefore, future steps include further long-term studies as well as larger randomized, controlled trials, with review of both entecavir and adefovir dipivoxil. Additional information regarding timing of antiviral therapy (first vs third trimester) regarding achievement of adequate viral suppression and prevention of MTCT, the optimal threshold of HBV DNA levels to treat patients with antiviral therapy, fetal and maternal safety, and viral resistance patterns are also warranted.

The American Association for the Study of Liver Diseases, the Asian-Pacific Association for the Study of the Liver, and the European Association for the Study of the Liver guidelines (Table) state that lamivudine, TDF, or telbivudine may be used in HBsAg-positive women with HBV DNA levels greater than 2×5 $\log_{10}$ IU/mL for the prevention of perinatal HBV transmission. Additionally, the Asian-Pacific Association for the Study of the Liver recommends TDF as the optimal choice for

chronic HBV treatment during pregnancy given its favorable resistance profile.

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