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Review

REVIEW

Management of chronic hepatitis B during pregnancy

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Abstract

Chronic hepatitis B is globally prevalent and is a major cause of cirrhosis and hepatocellular carcinoma. Despite immunoprophylaxis against hepatitis B in pregnancy, perinatal transmission still occurs in at least 10% of the children born to a mother with high level of viremia. Decisions regarding hepatitis B therapy during pregnancy must take into account the benefits and safety for both the mother and the unborn baby. In this review, we summarize the current treatment options for chronic hepatitis B with a focus on management during pregnancy and the evidence-based strategies to prevent vertical transmission of hepatitis B virus (HBV).

Key words: Chronic hepatitis B; pregnancy; nucleoside analogue; hepatitis B therapy

Introduction

Hepatitis B virus (HBV) infection is a significant public health problem worldwide and a major cause of chronic liver disease, cirrhosis and hepatocellular carcinoma. An estimated 257 million people globally have chronic hepatitis B (CHB), with the highest prevalence in the Western Pacific Region and Africa [1, 2]. According to the 2008 statistics, foreign-born Americans accounted for 13.6% of the total US population. The prevalence of CHB among all the foreign-born persons was 3.7% and the rates were significantly higher among Asian Americans (7.9%) and African Americans (11.8%) [3].

HBV is transmissible through perinatal, percutaneous and sexual exposure [4]. Among pregnant women in China and Thailand, the HBV prevalence rates are 7.6 and 6.2%, respectively [5, 6]. According to the statistics in the USA, there are approximately 23 000 pregnant women with CHB annually [7]. This short communication discusses the current treatment of CHB with an emphasis on the management of CHB during pregnancy.

Current treatment recommendations for CHB

The American Association for the Study of Liver Disease (AASLD) guideline recommends therapy for patients in the immune-active phase based on serial HBV and alanine aminotransferase (ALT) levels [8]. The updated guideline defines normal ALT as 35 U/L for males and 25 U/L for females [9]. Treatment is recommended for those with persistent elevation of ALT more than two times the upper limit of normal plus elevated HBV DNA. Elevated HBV DNA is defined as >20 000 IU/mL for HBeAg-positive immune-active and >2000 IU/ml for HBeAg-negative immune-active patients. Therapy is also recommended for persons with cirrhosis if HBV

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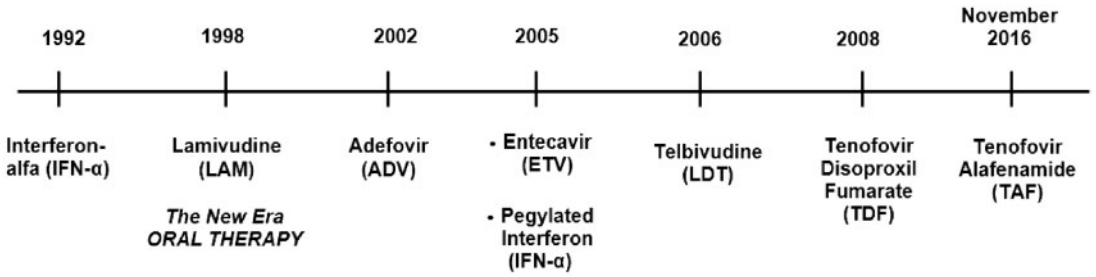

Figure 1. Timeline based on FDA approval of drugs for hepatitis B management.

Table 1. Forty-eight-week treatment results between TDF and TAF in HBeAg(+) and HBeAg(–) patients with chronic hepatitis B

48-week treatment results		HBeAg(+) ($n = 873$)			HBeAg(–) ($n = 426$)		
		TDF 300 mg ($n = 292$)	TAF 25 mg ($n = 581$)	*P*-value	TDF 300 mg ($n = 140$)	TAF 25 mg ($n = 285$)	*P*-value
Antiviral efficacy	HBV DNA <29 IU/mL	67%	64%	0.25	93%	94%	0.47
	ALT normalization Men: <30 U/L Women: <19 U/L	36%	45%	0.01	32%	50%	<0.001
Mean change in bone mineral density	Hip Z-score	–1.72%	–0.10%	<0.001	–2.16%	–0.29%	<0.001
	Spine Z-score	–2.29%	–0.42%	<0.001	–2.51	–0.88%	<0.001
Renal function	Mean changes in serum creatinine (mg/dL)	0.03	0.01	0.02	0.02	0.01	0.32
	Median estimated GFR (mL/min)	–5.4 (–12.6 to 3.0)	–0.6 (–8.4 to 7.8)	<0.001	–4.8 (–12.0 to 3.0)	–1.8 (–7.8 to 6.0)	<0.01

TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; HBV, hepatitis B virus; ALT, alanine aminotransferase; GFR, glomerular filtration rate.

DNA is >2000 IU/mL, regardless of the ALT level. There are additional factors that influence the decision to treat patients who do not meet the ALT and HBV DNA treatment criteria, including the presence of significant histological disease, family history of hepatocellular carcinoma and presence of extra-hepatic manifestations independently of liver disease severity.

At present, there are eight therapeutic agents approved by the Food and Drug Administration (FDA) for CHB. These include standard interferon-alpha, pegylated interferon-alpha and six oral nucleoside analogues: lamivudine, adefovir, telbivudine, tenofovir disoproxil fumarate (TDF), entecavir and tenofovir alafenamide (TAF) [10]. TAF is a new prodrug of tenofovir that was first approved by the FDA in November 2016. A brief overview of the medications for hepatitis B is shown in Figure 1.

Interferon-alpha has both antiviral and immunomodulatory properties [11]. Pegylated interferon-alpha has a longer half-life and a more convenient once-weekly dosing schedule. However, the use of interferons in CHB treatment is limited due to their significant side-effect profile and subcutaneous route of administration. Potential side effects include, but are not limited to, flu-like symptoms, psychiatric disturbances, cytopenia, weight loss and autoimmune disorders [8].

The availability of oral nucleoside analogues marked a new era of CHB therapy. According to the AASLD treatment guideline for CHB [8], entecavir and tenofovir are recommended as first-line oral therapy due to their efficacy and excellent drug-associated resistance profile. There are reports that tenofovir and entecavir, by long-term viral suppression, lead to regression of hepatic fibrosis and decrease the risk of hepatocellular carcinoma [8, 10, 12]. Lamivudine, adefovir and telbivudine, on the other hand, have limited clinical use due to the development of drug resistance with prolonged use. It is important to note that lamivudine and entecavir have potential cross-resistance [12]. TDF or TAF, therefore, is a preferred treatment choice for lamivudine-experienced patients.

Comparisons between TDF and TAF

Tenofovir is a nucleotide analogue with limited oral bioavailability that inhibits reverse transcription in HBV. TDF, an oral prodrug of tenofovir, was first approved for the treatment of CHB as a monotherapy in 2008 [8]. TDF is rapidly converted into tenofovir systemically after intestinal absorption, and circulating tenofovir exhibits an exposure–response relationship for antiviral activity [13, 14]. TDF has demonstrated potent antiviral activity in patients with chronic HBV infection with no resistance with prolonged use. Renal toxicity and reduction in mineral bone density were noted in susceptible patients. TAF is a phosphonamide prodrug of tenofovir that is more stable in plasma than TDF. TAF has approximately 90% lower circulating levels of tenofovir relative to TDF at therapeutically active doses. In contrast, TAF provides higher intracellular levels of the active phosphorylated metabolite tenofovir-diphosphate to HBV-infected hepatocytes [13–16]. The distinct metabolism of TAF offers an improved safety profile compared with TDF.

TAF was formulated to deliver the active metabolite directly to the liver cells more effectively at a lower dose compared to TDF. TAF was proven to have a similar efficacy to TDF in HBV DNA suppression at Week 48 in two phase 3 clinical trials evaluating patients with HBeAg-positive and HBeAg-negative CHB, respectively [16, 17]. TAF-treated patients were noted to have higher rates of ALT normalization as defined by 30 U/L for men and 19 U/L for women. By reducing systemic exposure, patients treated with TAF also had lower bone and renal toxic effects. The key efficacy and safety results are summarized in Table 1. The side effects were generally mild and were similar in both treatment groups. Longer observations are necessary to confirm these encouraging treatment outcomes with TAF. Currently, there are insufficient data to recommend TAF for patients with decompensated hepatic impairment.

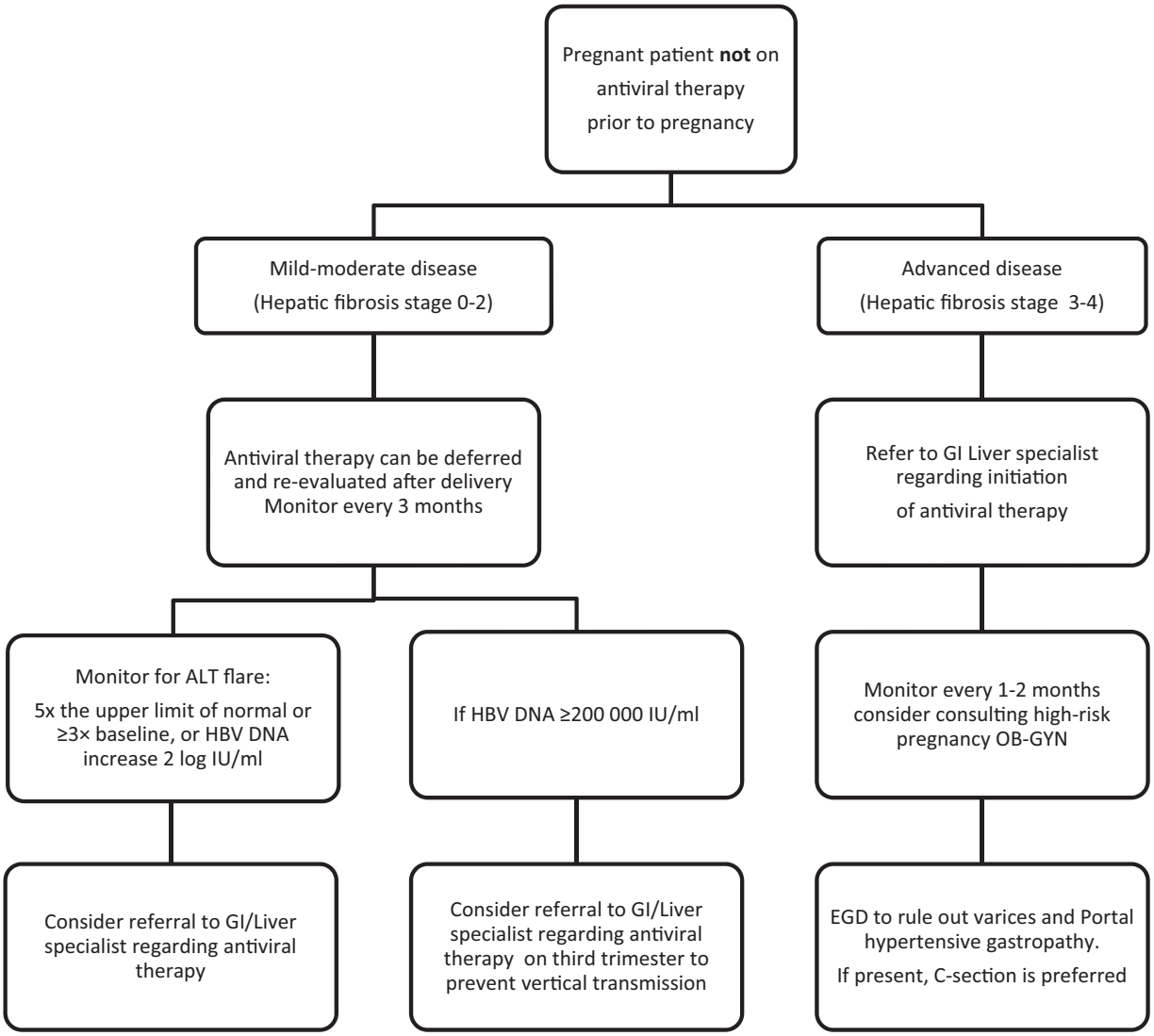

Figure 2. Management of pregnant women not on antiviral therapy prior to pregnancy.

Management of hepatitis B during pregnancy

For women of childbearing age who plan to become pregnant, the decision to initiate therapy needs to take into account the potential impact on the fetus. For pregnant patients without active or advanced chronic HBV infection, antiviral therapy can be deferred [9, 12] (Figure 2). Reactivation of HBV can occur during pregnancy and postpartum periods. It is believed that cell-mediated immunity is suppressed during pregnancy to prevent the rejection of the semi-allogenic fetus [18]. These immune responses are reversible during the post-partum period. These alterations in immune regulation likely contribute to increased HBV replication and elevated levels of aminotransferases during pregnancy and the postpartum period [18]. Chang *et al.* [19] retrospectively evaluated HBV DNA and ALT changes during pregnancy and postpartum among women with CHB. A flare in HBV DNA was defined as a minimum increase of 2 $\log_{10}$ IU/mL. ALT flare was defined as five times the upper limit of normal (ULN; 19 U/L) or at least three times the baseline value, whichever was higher. Severe flares were defined as an increase of 2 log IU/mL in HBV DNA and ALT ≥10 times ULN (≥190 U/L). With these definitions, HBV DNA flares were observed in 9% of the patients during pregnancy and 4% during postpartum. Flares in ALT (99–2522 U/L) were observed in 6% during pregnancy and 10% within the first 3 months of delivery. Hepatitis flares were generally asymptomatic, but one patient developed hepatic decompensation associated with the flare. It is generally reported that ALT levels increase during late third trimester or early postpartum [20]. In the study by Chang *et al.* [19], about 50% of ALT flares were observed during the second trimester or earlier. Clinical parameters such as HBV DNA, ALT, age, HBeAg positivity, gravida and parity were not identified as predictors of hepatitis flares in both univariate and multivariate analyses.

HBV and ALT flares during pregnancy are unpredictable and can be severe. Frequent monitoring during pregnancy and up to 6 months postpartum is recommended so antiviral therapy can be initiated in a timely manner. There is no consensus on the management of HBV in pregnant women with hepatitis flare. It is the authors' opinion to consider starting therapy if ALT levels persist to at least three times the baseline level or if the flare is associated with any abnormal hepatic function tests (Figure 2).

If a woman on antiviral therapy becomes pregnant, careful consideration needs to be made on whether to switch or to continue antiviral therapy. In a study of 400 women with HBV-

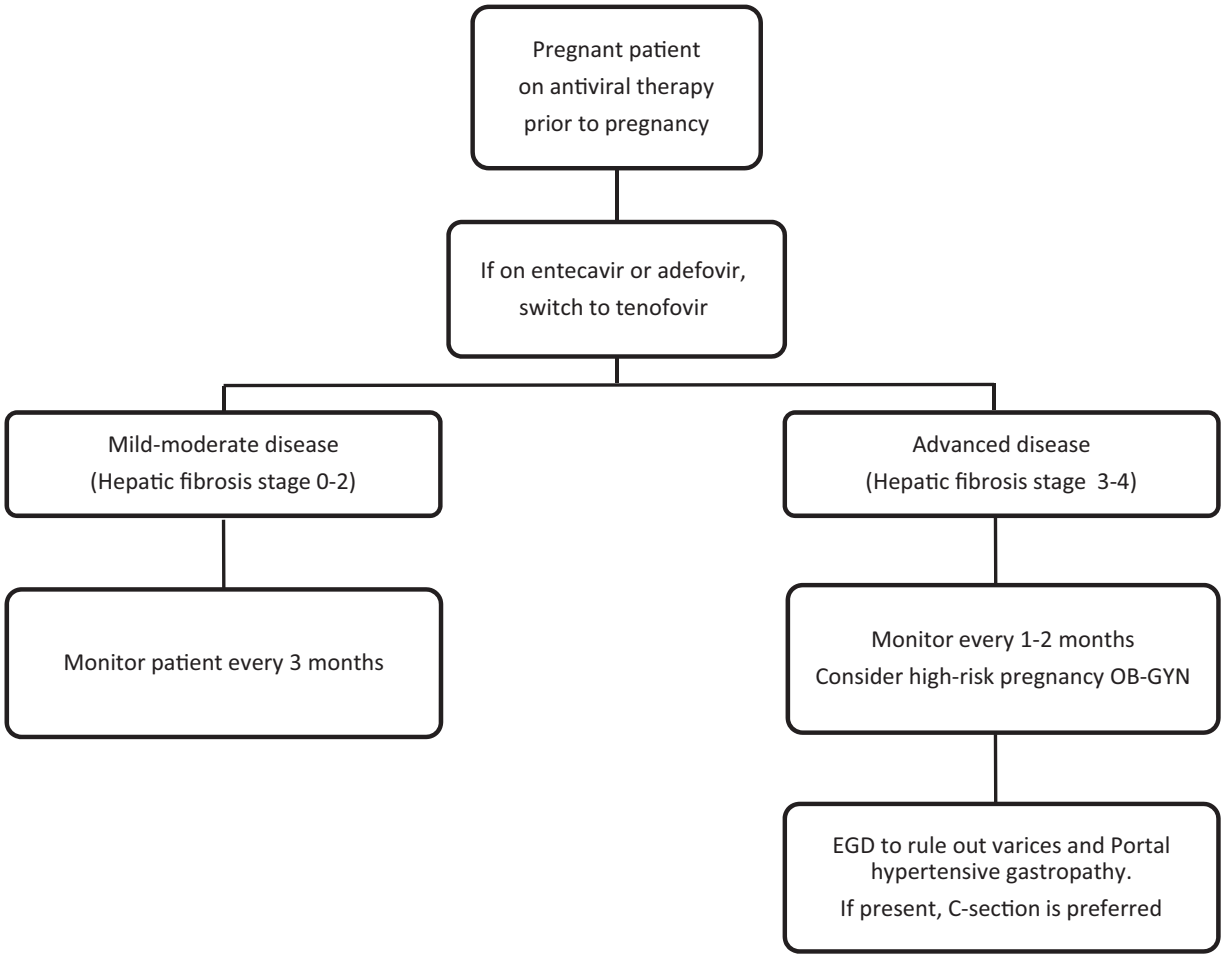

Figure 3. Management of pregnant women on antiviral therapy prior to pregnancy.

related cirrhosis, 15% experienced flares during pregnancy and risks for maternal morbidity and fetal death were estimated to be 1.8 and 5.2%, respectively []. In another study of 12 patients who discounted therapy during pregnancy, 8 patients experience flares and 6 patients experience a 5-fold increase in the levels of liver enzymes [21]. Hence, it is important to continue antiviral therapy in pregnant patients with advanced Stage 3 to 4 hepatic fibrosis (Figure 3).

Regardless of whether the women are on antiviral therapy, close monitoring during pregnancy and early postpartum is necessary, since ALT and HBV flares could occur in both treated and untreated women [19]. A number of treatment guidelines stated that breastfeeding is not a contraindication for patients on TDF therapy. Oral nucleotides including TDF are known to be excreted in the breast milk in low quantities [22]. Discretion and caution, therefore, should be exercised regarding the use of antiviral therapy during breastfeeding.

Strategies to prevent perinatal transmission of HBV

In endemic regions, the incidence of vertical transmission of HBV due to exposure to maternal blood at the time of delivery remains high [23]. Prior to the era of postnatal passive and active immunization, the rates of perinatal transmission for women with HBeAg (+) and HBeAg (–) CHB were 70–90 and 25%, respectively [24, 25]. It is recommended that babies born to mothers with CHB receive an HBIG dose of 0.5 mL intramuscularly and a first dose of HBV vaccine within 12 hours of birth [26]. A combination of postnatal passive and active immunization reduces the rate of mother-to-child transmission from 90 to 10%. There are, however, accumulative reports that, despite immunoprophylaxis, about 10–30% of the infants born to mothers with HBV DNA levels greater than 1 million copies/ml or 200 000 IU/ml still acquired HBV [27]. Approximately 85–90% of vertically infected newborns will develop CHB [28]. AASLD, therefore, recommended initiating antiviral therapy for women with HBV DNA >200 000 IU/mL during the third trimester of pregnancy to further reduce the chances of perinatal transmission [8, 9]. Other considerations for starting antiviral therapy include threatened preterm labor, prolonged uterine contractions and a child who failed immunoprophylaxis previously [29].

Lamivudine has been used to prevent perinatal transmission. A randomized–controlled clinical trial reported that the HBV seropositive rate in infants was lower in the lamivudine-treated group (18%) compared to the placebo group (39%) [30]. The HBV seropositive rates in both the treatment and placebo groups, however, appeared higher compared to other studies. There was concern about the low resistance barrier profile of lamivudine. In the event that resistance to lamivudine develops, antiviral therapy needs to be switched to TDF [31]. Telbivudine has been shown to be efficient in preventing perinatal transmission of HBV in highly viremic and HBeAg-positive pregnant patients. He *et al.* [32] described a study involving

94 mothers newly diagnosed with CHB in the first trimester of pregnancy. Twenty-seven and 32 patients were treated with lamivudine and telbivudine, respectively, and 35 received no treatment. The authors reported that perinatal transmission at postpartum Week 28 was significantly lower in the treated group ($P = 0.028$). Lamivudine and telbivudine were well tolerated in the mothers except for mild creatine kinase elevation in the telbivudine-treated group. Telbivudine has been reported to cause creatine kinase elevation and myopathy in selective patients [30]. Similarly to lamivudine, telbivudine is also associated with a low resistance barrier profile.

Pan *et al.* [29] evaluated the role of TDF in preventing HBV transmission in mothers with high viral load. In that study, 200 HBeAg-positive pregnant woman with HBV DNA >200 000 IU/mL were randomized in a 1:1 ratio to either a treatment or a control arm. Patients in the treatment arm received TDF 300 mg daily from 30–32 weeks of gestation until Week 4 postpartum. Patients in the control arm were provided with similar care and frequent clinical visits without antiviral therapy. Mothers in both arms were followed until Week 28 postpartum. All the infants received their first dose of HBV vaccine and hepatitis B immunoglobulin (HBIG) shortly after birth. The rate of mother-to-child transmission was significantly lower in the TDF-treated group than in the control group. In the intention-to-treat analysis, the transmission rate was 5% with TDF compared to 18% without treatment ($P = 0.007$). In the per-protocol analysis, the rate was 0% with TDF vs 7% without treatment ($P = 0.01$). In both the TDF and control groups, the birth-defect rates were low, at 2 and 1%, respectively ($P = 1.00$).

Recently, a multicenter, double-blind study of TDF versus placebo in Thailand did not show superiority of TDF in preventing perinatal transmission [33]. Of note, all the infants in both groups received HBIG and the median time of HBV vaccination was 1.2 hours after birth. This provided a clue that early administration of HBV vaccine within 2–4 hours after birth may be critical to prevent HBV transmission. This vaccine strategy, however, needs to be validated, especially for mothers with HBV DNA >8 $\log_{10}$ IU/mL, and its feasibility in various clinical settings needs to be determined. Currently, antiviral therapy should be considered for high-viremic pregnant women to reduce perinatal transmission as recommended by the AASLD guidelines.

Choice of antiviral therapy during pregnancy

Prior to the approval of TAF, entecavir and TDF were front-line therapy for CHB. Entecavir, however, is contraindicated in pregnancy use due to its significant carcinogenic potential in animal studies [8, 9]. There are sufficient safety reports on the safety of TDF use during pregnancy [34]. TDF is increasingly recommended due to its lowest risk of viral resistance with continuous therapy [8, 9]. In the prospective, voluntary reporting Antiretroviral Pregnancy Registry (APR) with 800 live births, there is no increased incidence of congenital anomalies associated with TDF [24]. TDF, however, has been associated with loss of bone mineral density [35, 36]. This raises the concern of the effect of TDF on the bone mineral content of the infants born to mothers taking TDF during pregnancy. In a study comparing 74 TDF-exposed vs 69 TDF-unexposed pregnant women, infants with *in utero* tenofovir exposure had a significantly lower bone mineral content than infants without *in utero* tenofovir exposure, even after controlling for maternal age at delivery, use of tobacco during pregnancy, infant race (black vs non-black), gestational age, length, age at dual-energy X-ray absorptionmetry (DXA) scan and clinical site [35]. The clinical consequences of these results are unknown and further research is necessary to determine the long-term growth and bone health of these infants.

Given the improved safety of TAF on bone mineral density and renal function, it appears to be an attractive alternative treatment option for pregnant women. Currently, there is no clinical recommendation on TAF use in pregnancy, though a clinical trial is ongoing to evaluate its efficacy and safety in this special HBV population. Embryonic fetal development studies performed in rats and rabbits revealed no evidence of TAF-related impaired fertility or harm to the fetus according to its preclinical evaluations. Ongoing and further studies on TAF will, hopefully, establish its safety profiles in both pregnant women and the newborns.

Conclusion

Management for HBV infection in pregnancy is complex, for the wellbeing of both the mother and the infant needs to be considered. With a careful, individualized treatment plan, successful pregnancy with healthy offspring can be achieved for women with CHB. The decision to initiate antiviral therapy depends on the severity of the liver disease of the woman and also the risk of perinatal transmission of HBV. Timely administration of HBV vaccine and HBIG is critical to break the chain of vertical transmission. Despite immunoprophylaxis, about 10–30% of the infants born to mothers with a high level of viremia are still at risk of acquiring HBV infection. Current treatment guidelines recommend initiating antiviral therapy during the third trimester of pregnancy for women with HBV DNA levels greater than 200 000 IU/mL to further reduce the risk of perinatal transmission. TDF is the preferred choice for this indication. Since pregnancy-associated hepatitis B reactivation can occur for both treated and untreated women, close monitoring is essential during pregnancy and for at least 6 months after delivery.

Conflict of interest statement: none declared.

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