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Management of hepatitis B in special populations

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A B S T R A C T

Special populations infected with chronic HBV include those with decompensated cirrhosis, coinfections (HIV, HCV, HDV), hemodialysis and renal failure, immunosuppressed including transplant patients, children and women in pregnancy. These populations differ in their natural history and risk for liver-related complications, the indications for anti-HBV therapy as well as the recommendations regarding the HBV drugs used, duration of therapy and anticipated endpoints. Reflecting the special populations with substantive changes in management in recent years, this review focuses on HBV–HIV coinfected patients, immunosuppressed patients at risk for reactivation, liver transplant recipients and pregnant women. Management of women in the context of pregnancy and post-partum requires consideration of risks to mother and fetus/infant, including the risk of mother-to-child transmission. HBV–HIV coinfected patients require initiation of treatment concurrent with their HIV therapy and the HBV drugs used must by selected to minimize HIV and HBV resistance long-term. Increasing recognition of the risk for HBV reactivation with immunosuppressive therapy has led to recommendations to use prophylactic HBV therapy in patients with moderate to high risk of reactivation. Liver transplant recipients with HBV require life-long therapy to prevent or treat HBV infection but with current therapies, graft and patient survival are excellent.

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The natural history of chronic hepatitis B, risk for disease progression and liver-related complications can be altered by co-existing conditions or comorbidities. These “special populations” include those with decompensated cirrhosis, coinfections with hepatitis viruses or HIV, renal failure, immunosuppressed status including solid organ and stem cell transplant recipients, children and pregnant women. For these patient groups, the recommendations for treatment typically differ from those of the “standard” patient with chronic hepatitis B. Some of these special populations are reviewed in other sections (cirrhosis, hepatitis D virus). Here, we focus on those populations for whom indications for treatment and/or recommendations regarding specific drugs for treatment have recently occurred – specifically pregnant women, those with HIV coinfection, those receiving immunosuppressive therapy and liver transplant recipients.

HBV and pregnancy

Screening of pregnant women

Perinatal transmission is estimated to account for 50% of the global burden of chronic hepatitis B, and in endemic areas is the prime mode of perpetuating hepatitis B infection in the population [1]. Exposure to maternal blood or other secretions at the time of delivery is the primary risk with in utero transmission rare. Pregnancy-associated procedures such as amniocentesis may be an additional risk factor if maternal HBV DNA levels are high [2]. Infants exposed to hepatitis B have a high likelihood of developing chronic infection but combined active-passive immunoprophylaxis of infants reduces the rate of perinatally-acquired HBV from 90% to 10–30% [3]. For this reason, screening of all pregnant women is recommended with infants of HBsAg positive mothers provided active-passive prophylaxis [4]. The first dose of hepatitis B vaccine and HBIG should be administered within 12 h of birth, as delays increase the likelihood of prophylaxis failure. The WHO also recommends that women who are HBsAg positive have testing for hepatitis D virus (HDV). This has relevance primarily in management of the mothers, as the risk of perinatal transmission of HDV is low and active-passive prophylaxis for HBV will protect infants from HDV infection.

Natural history of HBV in pregnancy

Pregnancy is a unique immunologic period with immunologic tolerance to paternally derived fetal antigens resulting in altered immune responses at the maternal-fetal interface (i.e. the placenta) as well as at the systemic level. Alanine aminotransferase (ALT)

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Abbreviations

ALT	Alanine aminotransferase
ARV	Antiretroviral therapy
ETV	Entecavir
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
HBeAg	Hepatitis B e antigen
Ant-HBc	Hepatitis B core antibody
HDV	Hepatitis D Virus
HIV	Human immunodeficiency virus
LMV	Lamivudine
LT	Liver transplantation
NA	Nucleos(t)ide analogues
peg-IFN	Peginterferon
LdT	Telbivudine
TDF	Tenofovir disoproxil fumarate
TAF	Tenofovir alafenamide
WHO	World Health Organization
TNF	Tumor necrosis factor
HCC	Hepatocellular carcinoma
FTC	Emtricitabine
IU	International units

levels tend to be lower in the second and third trimester compared to first trimester [5]. HBV flares during pregnancy are infrequent. In a longitudinal study of US women who were not on antiviral therapy pre-pregnancy, only 6% experienced a ≥2-log increase in HBV DNA during pregnancy accompanied by ALT flares [6]. For women on antiviral therapy pre-pregnancy who stop treatment when pregnancy is diagnosed, viral rebound with ALT flare appears to occur more frequently (67% in one study) followed by spontaneous recovery in the vast majority [7].

Post-partum ALT flares are reported in 9–45% of women, mostly within 3 months of delivery [5,8,9]. The majority of flares were subclinical – although there are rare reports of hepatic decompensation, likely in women who had advanced fibrosis during pregnancy. Whether HBV DNA levels predict risk of flares is unclear [6,10]. The frequency of flares in women who stopped antivirals at or soon after delivery appears similar or slightly higher than women not treated with antivirals during pregnancy [11]. Continuation of antiviral therapy post-partum does not prevent flares [6,11] and most flares resolve without intervention.

Treatment considerations in women of child-bearing age

Antiviral drugs and safety in pregnancy

Three drugs have been studied widely and are recommended during pregnancy – tenofovir, telbivudine (LdT) or lamivudine (LMV) [12]. Using the prior (to 2015) FDA designation for drug safety in pregnancy, LdT and tenofovir are pregnancy class B agents, indicating available animal studies do not identify teratogenic effects. LMV is a class C agent, based on some first trimester teratogenic effects in rabbits, but there is substantial human data supporting its safety in pregnancy. Of the three options, only tenofovir should be used as it is associated with lowest risk of viral resistance in women needing continuous therapy. Importantly, the published experience is with tenofovir disoproxil fumarate (TDF). The safety of the new formulation, tenofovir alafenamide (TAF) has not been assessed in pregnancy, though studies in HIV–HBV infected women are ongoing.

Since the risk period for teratogenicity is primarily the first trimester, minimizing exposures to non-recommended antivirals during the first trimester should be the goal. The Antiretroviral Pregnancy Registry is an international voluntary, drug exposure-registration registry of congenital malformations in infants of women exposed to antiretrovirals and antivirals in pregnancy. In the most recent analysis, 12,499 women were exposed to LMV, 4837 to TDF, 9 to LdT and 3 to TAF. The rate of birth defects among women with first trimester exposures was 3.06% (95% CI 2.60–3.62) for LMV and 2.23% (95% CI: 1.73–2.83%) for TDF, which is similar to that of general population at 3% [13]. A recent systematic review, which included mostly women exposed to LMV and TDF, found no significant differences in the congenital malformation rate, prematurity rate, and Apgar scores in women receiving antivirals during pregnancy versus untreated controls [14].

There has been concern regarding the effects of longer-term exposures to TDF on infant bone mineral density and bone growth. As most studies were conducted in TDF-exposed infants of HIV-infected mothers, it is unclear how accurately these findings translate to TDF-exposed infants of HBV-infected mothers [15–19]. Further, whether TAF can mitigate any potential risk to infant bone health is unknown at this time.

Pre-pregnancy planning and HBV therapy

The criteria to initiate antiviral therapy in women of child-bearing age are the same as any person with chronic hepatitis B. Women with elevated ALT levels and elevated HBV DNA levels (>2000 IU/mL or >20,000 IU/mL depending on HBeAg status) warrant consideration of antiviral therapy [12,20,21]. An assessment of disease severity is important. Women with mild disease can be deferred until after pregnancy. Those with advanced fibrosis/cirrhosis warrant treatment independent of ALT levels. In choosing therapy for women of child-bearing age, a discussion of the effects of the different antiviral drugs on a future pregnancy should be included. Peg-interferon may be an attractive option for women seeking a finite treatment course prior to starting their family. If nucleoside analogues (NAs) are used, the best option is TDF if long-term therapy is anticipated. ETV can be used but with the knowledge that a change of therapy to TDF should be done prior to conception.

For women on antiviral therapy who wish to stop in order to conceive, the risks of discontinuing therapy and experiencing a flare of HBV warrant careful review. Women with advanced fibrosis should be counseled to remain on antiviral therapy throughout their pregnancy and post-partum due to the concerns for decompensation in the context of an ALT flare. If antivirals are stopped, monitoring of ALT and HBV DNA levels at regular intervals (e.g. monthly) are recommended to insure HBV flares can be appropriately managed.

Management of women during pregnancy

Women on antiviral therapy who become pregnant

For women on antiviral therapy who become pregnant, discussion of the pros and cons of stopping treatment is essential. Among women who may have stopped antivirals for conception or to avoid exposures of drugs during the first trimester when risk of teratogenicity is highest, resumption of antivirals in the second trimester can be undertaken if there is strong clinical indication. For those stopping treatment, without a strong clinical indication to restart antiviral therapy during pregnancy, the HBV DNA level