Chapter 10

Current Management Strategies in Hepatitis B During Pregnancy

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Additional information is available at the end of the chapter

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Abstract

Hepatitis B virus (HBV) infection remains a major health problem worldwide and a major risk factor for end-stage liver disease and hepatocellular carcinoma. Notable differences of chronic hepatitis B prevalence were observed in geographic area. In highly endemic areas, at least 50 % of HBV infections are most commonly acquired either perinatally or in early childhood, during the first 5 years of life. The prevalence of chronic HBV infection in pregnant women is expected to mirror those in the general populations of each geographic area. Chronic hepatitis B during pregnancy is associated with high risk of maternal complications and an increased risk of mother-to-child transmission (MTCT). Thus, chronic hepatitis B during pregnancy can now be considered an important contributor to new HBV infections and to the global burden of disease. As a result, HBV infection during pregnancy requires management strategies for both the mother and the fetus/neonate, including prevention/elimination of MTCT and lessening the HBV effects on maternal and fetal health. This chapter will review current management strategies for hepatitis B in the pregnancy and the postpartum period, including special considerations on the effects of pregnancy on the course of HBV infection, MTCT, and antiviral therapy during the pregnancy.

Keywords: hepatitis B virus, pregnancy, mother-to-child transmission, disease burden, antiviral treatment, HBV vaccination, hepatitis B immune globulin (HBIG)

1. Introduction

Hepatitis B is caused by hepatitis B virus (HBV), a partially double-stranded DNA virus, member of the Hepadnaviridae family. The hepatitis B virion is a 42-nm particle composed

of a 27-nm nucleocapsid consisting of the hepatitis B core antigen (HBcAg) surrounded by an outer lipoprotein coat envelope containing the hepatitis B surface antigen (HBsAg) [1, 2].

To date, 10 HBV genotypes (A–J) have been defined based on intergroup divergence of above 8 % in the complete nucleotide sequence and over 30 subgenotypes. The genotypes show heterogeneity in their global geographic distribution and have also been associated with different clinical features and different responses to antiviral therapy [3–6].

HBV infection remains a major health problem worldwide and a major risk factor for end-stage liver disease and hepatocellular carcinoma. Two billion people worldwide have been infected with HBV, and more than 240 million people have chronic hepatitis B infection defined as HBsAg positive for more than 6 months. Despite the fact that in many countries HBV infections have declined substantially because of effective prevention strategies, more than 780,000 people die every year worldwide due to HBV complications, including cirrhosis and liver cancer [2].

HBV infection is transmitted by percutaneous and mucous membrane *via* blood or infected body fluids [7]. HBV mother-to-child transmission (MTCT), defined as HBsAg positivity at 6–12 months of life in an infant born to an infected mother, has been recognized as a major mode of transmission and at the same time the most important phase for the chronic hepatitis B prevention. In Asia, up to 50 % of new cases of HBV infection are due to MTCT [8–10]. In Europe, MTCT is the most important and frequent transmission route of HVB infection, which accounted for 41.1 % of all cases, according to the results of the first enhanced surveillance data collection of HVB infections across 30 countries of the European Union and the European Economic Area [11].

Infants born to HBsAg-positive mothers who do not become infected perinatally remain at risk of HBV infection during early childhood [12]. More than one third of patients with HBV acquired the infection during the perinatal period or in early childhood, even in low-endemic areas [13]. In highly endemic areas, at least 50 % of HBV infections are most commonly acquired either perinatally or in early childhood, during the first 5 years of life [2]. Moreover, the rate of chronicity is about 90 % for perinatally acquired HVB infection or during the first year of life, 30–50 % in infected children between ages 1 and 6 years, and 5–10 % in children over the age of 6 years and in adults [2, 14].

Thus, chronic hepatitis B during pregnancy is now an important contributor to the new HBV infections and to the global burden of disease.

2. Epidemiologic aspects of HBV infection in pregnant women

Notable differences of chronic hepatitis B prevalence were observed by geographic area, with the highest endemicity levels in the sub-Saharan Africa and East Asia (5–10 %) and low prevalence (<1 %) in the United States (USA), Canada, and Western Europe. High rates of prevalence have also been found in the southern regions of Eastern and Central Europe [2, 15].

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According to the technical report of the European Centre for Disease Prevention and Control (ECDC), based on literature review, the prevalence of HBsAg in the general population ranged from 0.1 to more than 7 % by country. Countries in the central or southern part of the Europe (EU) have a higher prevalence of HBV infection than countries in the northern or western part of the EU. Thus, Romania, Greece, and Turkey have a high HBV prevalence (>2 %); Italy has medium HBV prevalence (>1 and ≤2 %), while Belgium, France, Spain, Germany, the Netherlands, Slovakia, Sweden, Switzerland, and the United Kingdom have a low HBV prevalence (≤1 %). Among countries with available data, Turkey has the largest number of HBV-infected individuals (national and regional estimates ranged from 2.5 to 9.0 % in adults and 1.7 to 2.7 % in children only), followed by Romania (5.6 %) [16].

The prevalence of chronic HBV infection in pregnant women is expected to mirror those in the general populations of each geographic area. Thus, in higher endemicity areas, rates are proportionately higher [9].

In the United States, a country of low endemicity, estimated chronic HBV infection prevalence in pregnant women is 0.7–0.9 % [17]. In Europe, the chronic HBV infection prevalence in pregnant women is generally higher than in the general population (0.1–4.4 %) in countries where both estimates were available (e.g., Germany, Greece, Ireland, Italy, the Netherlands, and Slovakia), according to the ECDC study. This difference in prevalence can be attributed to the fact that migrant women, whom have a relatively high HBV infection prevalence, are better represented in pregnancy studies than in general population studies. Conversely, Spain reported in Catalonia in 2004 a lower prevalence of chronic hepatitis B in pregnant women than the prevalence in the general population in the same region in 2002 (0.7 %), attributing these aspects to the higher vaccination rate [16]. In France, the prevalence of chronic HBV infection is about 1 % in pregnant women [18]. In Denmark, country where all pregnant women have been screened for HBV since November 2005, the overall prevalence of HBV infection among pregnant women has increased from 0.11 % in 1971 to 0.26 % in 2007. In the same period, the prevalence among pregnant native Danes decreased from 0.11 to 0.01 % [19].

Available data suggest a wide variation in prevalence of chronic HBV infection among pregnant women globally. However, there are insufficient epidemiological data and limitations to estimate the epidemiology of HVB infection among pregnant women globally.

3. Serological markers of HBV infection

Measurement of several HBV antigens and/or antibodies plays an important role in diagnosis, assessment, and monitoring the disease progression and its response to treatment.

There are three clinical useful antigen-antibody groups used in the serological diagnosis of HVB:

1. Hepatitis B surface antigen and antibody: antigen (HBsAg) and antibody to HBsAg (anti-HBs)

2. Core antigen and antibodies: antigen (HBcAg does not appear in the blood) and antibody to HBcAg (anti-HBc), IgM antibody subclass of anti-HBc (IgM anti-HBc), and IgG antibody subclass of anti-HBc (IgG anti-HBc)
3. Hepatitis B e antigen (HBeAg) and antibody to HBeAg (anti-HBe)

Additionally, the presence and concentration of circulating HBV DNA can also be tested [20–22].

HBsAg is the serological hallmark of both acute and chronic forms of HBV infection and the most commonly used diagnostic and blood screening marker for HBV infection. It usually appears in serum 1–10 weeks (average, 4 weeks) after acute exposure to the virus, and its persistence for six months or more implies progression to chronic HBV infection. The presence of HBsAg indicates that the person is infected with HBV and is therefore potentially infectious. More than 95–99 % of adults with acute HBV infection will recover spontaneously, without antiviral therapy [23, 24].

In patients that recover completely from their HBV infection, HBsAg usually becomes undetectable after four to six months, and its disappearance is followed several weeks later by the appearance of anti-HBs. Therefore, there is a gap ("window period") of several weeks to months between the disappearance of HBsAg and the appearance of anti-HBs, and during this period, the detectable marker of HBV infection is anti-HBc. The persistence of anti-HBs for a lifetime provides long-term immunity against HBV. Therefore, the presence of anti-HBs in serum attests to previous HBV exposure and acquired immunity. In some patients, anti-HBs may not become detectable after disappearance of HBsAg. These patients do not appear to be susceptible to recurrent infection [20, 23, 24].

Total anti-HBc (IgM and IgG) appears before anti-HBs, and its presence in serum attests both past exposure and current HBV infection. Its presence during the “window period” makes it a reliable indicator of HBV infection, in the absence of other HBV markers [25].

IgM anti-HBc develops in acute HBV infection and may usually persist for four to six months if the infection resolves [20, 22]. Although it is considered a reliable serologic marker for acute infection, IgM anti-HBc can also become positive during a chronic hepatitis B flare in patients who have long-standing hepatitis B [26, 27].

A negative IgM anti-HBc in conjunction with a positive HBsAg likely suggests a chronic HBV infection. As a result, routine testing for IgM anti-HBc is not generally recommended to screen for acutely infected patients [28, 29].

IgG anti-HBc develops in the late acute phase of infection and generally remains detectable for lifetime [20]. IgG anti-HBc may be the only serologic marker remaining in patient serum who recover from acute HBV infection. The presence of IgG anti-HBc can indicate progression to chronic disease [22].

HBeAg is a viral soluble protein that develops in the serum of persons with acute or chronic HBV infection. HBeAg appears in serum early during acute HBV infection and usually disappears about three weeks before HBsAg disappears. Persistence of HBeAg three or more months after the onset of illness indicates a carrier state and the risk of developing chronic

HVB. The HBeAg presence in the serum of HBV carriers and chronic hepatitis B patients indicates greater infectivity and a high level of viral replication [20, 30].

The small-size soluble HBeAg can cross the placental barrier from the mother to the fetus especially through villous capillary endothelial cells. The maternal HBeAg-positive serological status and high serum HBV DNA levels increase the risk of MTCT. By contrast, the absence of the HBeAg in serum is associated with lower levels of viral replication and with a significantly lower risk of intrauterine HBV transmission. The infants born to HBeAg-positive mothers have up to 90 % chance of acquiring perinatal HBV without prophylaxis [13, 14, 31, 32].

Anti-HBe appears in the resolution phase of the disease, when HBeAg disappears. Its presence correlates to a decreased infectivity. A seroconversion of HBeAg to anti-HBe marks a transition to the inactive carrier state in the majority of cases [20].

Spontaneous or treatment-induced HBeAg seroconversion is associated with lower rates of disease progression [33].

In addition to viral antigens and antibodies detected or measured, serum HBV DNA can also be measured both qualitatively and quantitatively (HBV viral load). HBV DNA is the most sensitive and specific marker of viral replication [29].

Serologic pattern of acute HBV infection is characterized by the transient presence of HBsAg (<6 months) and IgM anti-HBc. HBeAg and HBV DNA are also present during the initial phase of infection. The disappearance of HBV DNA, HBeAg to anti-HBe seroconversion, and loss of HBsAg or HBsAg to anti-HBs seroconversion designate recovery. The presence of IgG anti-HBc in the absence of HBsAg usually indicates a past HBV infection, while the presence of anti-HBs only reveals immunity to HBV infection after vaccination [20, 22, 25].

Three standard tests (HBsAg, anti-HBs, and anti-HBc) are usually indicated to determine if a person is currently infected with HBV, has recovered from HBV infection, or is susceptible to HBV infection [20].

Combinations of serologic HBV markers are used to identify different phases of HBV infection (**Table 1**).

Serological markers	Results	Interpretation
HBsAg	Negative	Never infected. Susceptible
Total anti-HBc	Negative	Vaccination should be recommended
Anti-HBsAg	Negative	
HBsAg	Negative	Recovered from past infection and immune
Total anti-HBc	Positive	
IgM anti-HBc	Negative	
Anti-HBsAg	Positive	
HBsAg	Negative	Immune due to hepatitis B vaccination
Total anti-HBc	Negative	

Serological markers	Results	Interpretation
Anti-HBsAg	Positive	
HBsAg	Positive	Acute HBV infection
Total anti-HBc	Positive	
IgM anti-HBc	Positive	
Anti-HBsAg	Negative	
HBsAg	Positive	Chronic HBV infection
Total anti-HBc	Positive	
IgM anti-HBc	Negative	
Anti-HBsAg	Negative	
HBsAg	Negative	Interpretation of isolated detection of anti-HBc
Total anti-HBc	Positive	Resolved infection
Anti-HBsAg	Negative	Window period of acute HBV (anti-HBc-predominantly IgM)
		False-positive test results
		"Low level" chronic infection

Table 1. Most common serological profiles of HBV infection [20, 22, 28].

4. Mechanisms and predictors for MTCT of HBV infection

Perinatal transmission of hepatitis B is highest in mothers with acute hepatitis, especially in HBe-positive mothers in the third trimester (50–80 %), lower in mothers with anti-HBe (25 %), and lowest in carriers (5 %) [34].

The World Health Organization (WHO) defines "perinatal" as the time period starting at 22 completed weeks (154 days) gestation and ending seven complete days after birth [35]. However, the perinatal period is defined in various ways, and depending on the definition, it starts at the 20th–28th week of gestation and ends 1–4 weeks after birth [36]. The term MTCT is entitled and covers the transmission of all HBV infections from mother to her child during pregnancy (intrauterine transmission), childbirth, or after birth. As a result, there are three main possible routes for MTCT of HBV infection: transplacental transmission of HBV, transmission during delivery, and postnatal transmission during child care and breastfeeding [37].

Intrauterine transmission of HBV is considered the most important cause for the failure of passive-active immunoprophylaxis in preventing MTCT, although it is presumed to cause a minority of HBV infections [38]. The main risk factors for intrauterine HBV infection are maternal serum HBeAg positivity, high HBV DNA level, history of threatened preterm labor, and HBV presence in the villous capillary endothelial cells of the placenta. One of the proposed mechanisms involved in the HBV intrauterine transmission is the transplacental leakage of

HBeAg-positive maternal blood induced by uterine contractions during pregnancy and by the disruption of placental barriers. In addition, HBeAg can pass through the placenta via the "cellular route." Although the risk of fetal hepatitis B infection through amniocentesis is considered to be low, the maternal HBeAg status would be valuable in the counseling regarding risks associated with amniocentesis. Another possible route of HBV intrauterine transmission could be via germ cells, maternally or paternally dependent [14, 37, 39].

HBV transmission during delivery is recognized as the most important route of MTCT in endemic areas for HBV infection, as a result of exposure to maternal cervical secretions and maternal blood that contain HBV. There is no consensus regarding the effect of delivery mode on MTCT (vaginal delivery vs. cesarean section). While some studies suggest that cesarean section might reduce the risk of MTCT, other studies assert that the mode of delivery does not influence the rate of HBV transmission as long as all infants received both hepatitis B vaccine and hepatitis B immune globulin (HBIG) at birth [37].

There is little evidence that cesarean delivery prevents HBV transmission, and current guidelines do not recommend cesarean section to decrease the risk of MTCT. As for elective cesarean section (ECS), there are studies that show alike an absolute risk reduction of MTCT of HBV compared with immunoprophylaxis alone and studies that report no benefit to ECS. According to recent clinical guidelines of American College of Gastroenterology (ACG) concerning liver disease and pregnancy, validation studies are needed to determine the relative safety and efficacy of ECS and immunoprophylaxis versus immunoprophylaxis alone in reducing MTCT of HVB [40].

Although markers of HBV are detectable in breast milk from HBsAg-positive women, there is no evidence that breastfeeding is a risk factor for HBV infection if the infant received hepatitis B vaccine and HBIG. According to the WHO and the American Academy of Pediatrics recommendations, in infants who receive full immunoprophylaxis, breastfeeding in HBs-positive mothers is not a contraindication [9, 41, 42].

5. Clinical and laboratory features of HBV infection in pregnancy

The clinical manifestations of HBV infection may be variable in both acute and chronic diseases. In acute HBV infection, clinical manifestations usually range from anicteric hepatitis to icteric hepatitis, while in the chronic phase, manifestations range from an asymptomatic carrier state to chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Fulminant hepatic failure, most probably due to massive immune-mediated lysis of infected hepatocytes, is unusual but can occur in some cases. Extrahepatic manifestations may be present in both acute and chronic infections [25, 40, 42].

Testing for HBsAg should be performed in all women at the first prenatal visit, even if they have been previously vaccinated or tested, and repeated later in pregnancy if appropriate [25, 43].

The first step in assessing a woman presenting at any stage of pregnancy with acute or chronic HBV infection should be the same as with any nonpregnant patient: complete history, physical

Phase	ALT	HBV DNA	HBeAg	Notes
"Immune tolerant"	Normal	Elevated	Positive	Perinatal or early childhood-acquired HBV infection Patients are highly contagious Low spontaneous HBeAg loss Minimal liver inflammation and fibrosis
HBeAg-positive immune-active phase "Immune active"	Elevated	Elevated	Positive	Moderate-to-severe liver inflammation or fibrosis HBeAg to anti-HBe seroconversion possible, leading to "immune-control" phase
Inactive chronic hepatitis "Immune control"	Normal	Low or undetectable	Negative	Low risk for cirrhosis Minimal liver necroinflammation, variable fibrosis
HBeAg-negative chronic hepatitis "Immune escape mutant"	Elevated persistent or intermittently	Moderate to elevated	Negative	Generally in older persons Liver necroinflammation Risk for fibrosis or cirrhosis
"Reactivation" or "acute-on-chronic hepatitis" or HBeAg-negative immune reactivation phase	Elevated	Elevated	Negative	Spontaneously or precipitated by immunosuppressive therapy, transplantation, antiviral resistance, HIV infection, withdrawal of antiviral therapy Moderate-to-severe liver necroinflammation and fibrosis

Table 2. Phases of chronic hepatitis B [44–46].

exam, standard serological workup, laboratory test which should include assessment of liver disease activity and function, markers of HBV replication, and tests for coinfection with hepatitis C virus [8, 16, 40, 43, 44].

The clinical spectrum of acute HBV infection in pregnant women usually is not different from that of nonpregnant women; however, the risk of preterm delivery and low birth weight is higher than in the general population [9, 14, 42]. It seems that acute HBV infection does not increase mortality or have teratogenic effects [9].

Common symptoms of acute HBV infection in pregnant women are indistinguishable from those of nonpregnant, including upper quadrant discomfort, fatigue, nausea, vomiting,

diarrhea, headaches, myalgia, anorexia, low-grade fever, and jaundice. The icteric phase of acute viral hepatitis usually begins within 10 days of the initial symptoms and disappears about 4–12 weeks afterwards. Diagnosis is based on the detection of HBsAg and the presence of IgM anti-HBc. Recovery is accompanied by HBsAg clearance with seroconversion to anti-HBs, usually within 3 months. Concentrations of alanine and aspartate aminotransferase (ALT and AST) levels usually increase, with ALT typically higher than AST. In patients who recover, normalization of serum aminotransferases usually occurs within one to four months [20, 25, 42, 45].

Acute exacerbation or flare of hepatitis in chronic HBV infections can be present during pregnancy, and it may be difficult to differentiate from acute HBV infection. HBV testing with HBsAg and IgM anti-HBc is recommended in pregnant women presenting with acute hepatitis [40].

Most chronic HBV infections are asymptomatic and pregnancy is well tolerated. Some patients may complain of fatigue, anorexia, and nonspecific malaise. Significant symptoms will develop only if the liver disease progresses. Cirrhosis, condition usually associated with amenorrhea and infertility, is relatively uncommon in the younger age group of pregnant women, and severe cases are fortunately rare [9, 42, 45]. The chronic hepatitis B is usually mild in pregnant women but may flare at the end of pregnancy or shortly after delivery [9].

The natural history of chronic HBV infection consists of several phases of variable duration, which are not necessarily sequential (**Table 2**) [44–46]. Pregnancy is a hormone-induced immune-tolerant state, and there is limited understanding of the natural history of chronic HBV infection during pregnancy [47]. Increased levels of adrenal corticosteroids and estrogen hormones during pregnancy may be responsible for an increase in HBV viral load and a decrease in ALT levels. A postpartum decline in HBV DNA level, associated with increased ALT levels and active hepatitis, requires close monitoring of the mother [9, 42].

6. Current management strategies for chronic hepatitis B in pregnancy

HBV infection during pregnancy requires management strategies for both mother and fetus/neonate, including prevention/elimination of MTCT and lessening the HBV effects on maternal and fetal health [48, 49].

Current management strategies for hepatitis B during pregnancy include antenatal maternal screening for HBV infection, initial assessment of mother with HBV infection (severity of liver disease, level of viral replication, presence of comorbidities), prophylactic HBV vaccination and HBIG administration to all infants born to HBV-infected mothers as soon as possible after birth, the use of antiviral medications for pregnant women with chronic hepatitis B, safe delivery practices, and strengthened maternal and child health services [8, 40, 45, 50].

Few countries have national hepatitis strategies, plans, and budgets, and as a consequence, the WHO recently published a 5-year global health sector strategy on viral hepatitis. This

includes testing algorithms, strategies for hepatitis B, diagnosis and management of acute hepatitis B, as well as management of advanced liver disease [8, 45].

Antenatal screening for HBV infection in all pregnant women is a well-established, evidence-based standard of practice to prevent MTCT. Therefore, the first step is to identify all HBsAg-positive pregnant women in the first trimester by universal screening [45].

All pregnant women who are HBsAg positive should be assessed the same way as any non-pregnant individual: a complete history with special emphasis on risk factors for coinfection, physical exam and laboratory tests for assessment of liver disease activity and function, markers of HBV replication, and tests for coinfection (hepatitis C virus, hepatitis delta virus, or human immunodeficiency virus in those at risk) [24, 44, 48, 50].

Assessment of the severity of liver disease should include measurement of ALT, AST, alkaline phosphatase (ALP), gamma-glutamyl transpeptidase, total bilirubin, full blood count, serum albumin and globulins, prothrombin time, and an ultrasound examination. Assessment of the level of viral replication in chronic hepatitis B using quantification of serum HBV DNA and HBeAg and anti-HBe is an important step in determining the risk of MTCT and therefore in guiding antiviral therapy decisions and the need for surveillance [24, 44, 48, 50]. Elevated serum ALT and HBV DNA levels are strongly predictive of risk of liver complications [44].

According to the WHO Strategic Advisory Group of Experts, the currently recommended practice to reduce perinatal MTCT of HBV relies on the administration of HBV vaccine and, in some countries, concurrent administration of HBIG. The infants of all HBsAg-positive women should receive immunoprophylaxis with HBV vaccination ± HBIG. Hepatitis B vaccine and HBIG should be administered at different injection sites [45].

The timing of administration of the first dose of hepatitis B vaccine to infants in relation to birth is the most important factor in determining the efficacy of vaccination [41, 51]. As a result, the recommended timing of administration of the first dose of hepatitis B vaccine in newborns has evolved in the last decades, in order to optimize prevention of MTCT hepatitis B infections. The WHO recommends that all infants receive the hepatitis B vaccine as soon as possible after birth, within 24 h of the birth [2].

Passive immunization against hepatitis B with HBIG in conjunction with HBV vaccination may be of additional benefit for newborn whose mothers are HBsAg positive, particularly if they are also HBeAg positive [45]. According to the Centers for Disease Control, all preterm infants born to HBsAg-positive mothers and mothers with unknown HBsAg status must receive HBIG and hepatitis B vaccine within 12 h of birth [52].

Unfortunately, despite postnatal active-passive immunization of the newborns, MTCT of HBV still occurs, especially if the mother has very a high maternal concentration of HBV DNA, typically observed in HBeAg-positive women [45].

There are emerging data based on open-label nonrandomized studies which suggest that short-term maternal antiviral therapy used in pregnant women with stable liver disease during the third trimester may reduce the risk of MTCT occurring during the perinatal period, by lowering maternal viral load prior to delivery [24, 47].

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Current guidelines of the American Association for the Study of Liver Diseases (AASLD), ACG, European Association for the Study of the Liver (EASL), and Asian Pacific Association for the Study of the Liver (APASL) suggest or recommend antiviral therapy to reduce the risk of perinatal transmission of hepatitis B in HBsAg-positive pregnant women with a HBV DNA above 200,000 IU/mL [24, 44, 48, 50]. As for the WHO current position, the Guidelines Development Group did not make a formal recommendation on the use of antiviral therapy to prevent MTCT, due to the fact that key trials are still ongoing and there is a lack of consensus regarding the programmatic implications of a policy of more widespread antiviral use in pregnancy [45].

There are only three therapeutic antiviral agents studied and used for the treatment of chronic hepatitis B in pregnant women: lamivudine, telbivudine (nucleoside analogues (NAs)), and tenofovir disoproxil fumarate (nucleotide analogue). According to the US Food and Drug Administration classification of oral antiviral, based on the risk of teratogenicity in preclinical evaluation, only two drugs from the nucleoside/nucleotide analogues (NAs) class—tenofovir and telbivudine—are classified in risk category B (no risk in animal studies, but unknown in humans), while lamivudine, entecavir, and adefovir dipivoxil are classified as category C drugs (teratogenic in animals, but unknown in humans) [24, 44]. Additionally, tenofovir received category B classification based on data collected from human exposure [53].

Lamivudine, the first and the most studied NAs in pregnant women with chronic hepatitis B, is not considered an optimal choice for prevention of MTCT due to its poor antiviral activity and low barrier to resistance. Its administration, even for short periods, is associated with the selection of resistant mutants. Lamivudine reaches higher concentrations in amniotic fluid than in serum and has been found to be excreted in breast milk [49, 54, 55].

The results of small human pregnancy trials show that telbivudine reduces MTCT in highly viremic pregnant women and its use appears to be safe in late pregnancy [47].

Tenofovir is considered a preferred choice in pregnant women with chronic hepatitis B, due to its antiviral potency, the available safety data of use during pregnancy, and its better resistance profile [44, 45].

As for other antiviral drugs, the safety of entecavir in pregnancy is not known, and interferon (IFN) therapy is contraindicated during pregnancy [44, 45].

Antiviral therapy was started at 28–32 weeks of gestation in most studies, and therefore NAs starting from 28 to 32 weeks of gestation are recommended [24, 45]. A careful examination to exclude maternal systemic disorder and fetal anomalies is required prior to the administration of NAs [44, 50]. For pregnant women with immune-active chronic hepatitis B, monitoring therapeutic response to NAs, both serological and virological, as well as for potential side effects, should be based on recommendations for nonpregnant women [24, 44, 45]. Tenofovir therapy requires monitoring serum creatinine and serum phosphate levels every three months, due to potential nephrotoxicity. The risks of maternal liver disease, fetal development, HBV MTCT, and long-term plan for treatment should be discussed with pregnant women [24, 50].

Although there are no studies on the duration of NA therapy (cessation at delivery vs. after delivery), cessation of NA therapy (at delivery or 4–12 weeks after delivery) is recommended in females without ALT flares [24, 44, 45]. According to EASL guidelines, if NA therapy is given only for prevention of MTCT, it may be discontinued within the first 3 months after delivery [50]. If the anti-HBV therapy is discontinued during pregnancy or early after delivery, women need to be closely monitored for the risk of hepatic flares, especially after delivery [44, 50].

In certain situations, such as ALT flares detected during the treatment period, continuation of antiviral treatment after delivery is needed. As a result, this raises the issue of safety of NA therapy during breastfeeding. Due to limited data on the effect of these medications on infants, the safety of NA therapy during breastfeeding is considered uncertain [24, 50].

The safety of lamivudine and tenofovir during breastfeeding in HBV infection has not been well studied. Additionally, tenofovir and lamivudine concentrations in breast milk have been reported. However, due to its poor oral bioavailability, the breastfeeding infants are exposed to only small tenofovir concentrations [50].

According to drug labels, tenofovir disoproxil fumarate and lamivudine should not be used during breastfeeding. Breastfeeding is discouraged during maternal NA treatment according to APASL current guidelines, but in the case of ALT flares, continuation of antiviral may be indicated, depending on the liver disease status of mother [24]. A recent review of available data concluded that tenofovir and lamivudine should not be contraindicated during breastfeeding. However, there are insufficient data based on long-term studies to establish the safety of infant exposure to different antiviral therapies during breastfeeding [56].

7. Conclusions

Despite advancements in the prevention, diagnosis, and treatment of HBV infection, it remains a serious global health issue and one of major risk factors for end-stage liver disease and hepatocellular carcinoma. Given that chronic hepatitis B in pregnant women is an important contributor worldwide to the new HBV infections, most effective and sustainable measures are required for prevention of MTCT. Universal screening of pregnant women for HBsAg and passive and active immunoprophylaxis are important tools in MTCT of HBV. The causes of immunoprophylaxis failure in some infants are not yet not fully understood, and, therefore, studies are needed in order to clarify this issue. Longitudinal cohort studies are also required to determine the safety of infant exposure to different NA therapies during breastfeeding.

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