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MINIREVIEWS

Chronic hepatitis B in pregnant women: Current trends and approaches

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Abstract

Chronic hepatitis B (CHB) is a significant public health problem worldwide. The aim of the present review is to summarize the actual trends in the management of CHB in pregnant women. The prevalence of hepatitis B virus (HBV) infection in pregnant women is usually comparable to that in the general population in the corresponding geographic area. All women have to be screened for hepatitis B surface antigen (HBsAg) during pregnancy. Additional examinations of pregnant women with CHB may include maternal hepatitis B e antigen, HBV viral load, alanine aminotransferase level, and HBsAg level. The management of pregnancy depends on the phase of the HBV infection, which has to be determined before pregnancy. In women of childbearing age with CHB, antiviral therapy can pursue two main goals: Treatment of active CHB, and vertical transmission prevention. During pregnancy, tenofovir is the drug of choice in both cases. A combination of hepatitis B immunoglobulin and vaccine against hepatitis B should be administered within the first 12 h to all infants born to mothers with CHB. In such cases, there are no contraindications to breastfeeding.

Key Words: Chronic hepatitis B; Hepatitis B viral load; Pregnancy; Antiviral treatment;

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Core Tip: All women have to be screened for hepatitis B surface antigen (HBsAg) during pregnancy. Additional examinations of pregnant women with chronic hepatitis B (CHB) may include maternal hepatitis B e antigen, hepatitis B virus (HBV) viral load, alanine aminotransferase level, and HBsAg level. The management of pregnancy depends on the phase of the HBV infection, which has to be determined before pregnancy. During pregnancy, tenofovir is the drug of choice both for active CHB treatment and vertical transmission prevention. A combination of hepatitis B immunoglobulin and vaccine against hepatitis B should be administered within the first 12 h to all infants born to mothers with CHB.

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INTRODUCTION

Chronic hepatitis B (CHB) is a significant public health problem worldwide. According to the current estimation by the World Health Organization (WHO), in 2015 about 257 million people in the world were living with CHB[1,2]. The geographic distribution of CHB is highly heterogeneous. There are regions with high (more than 8%), medium (2%-8%) and low (less than 2%) levels of hepatitis B (HB) prevalence. The course of CHB varies from asymptomatic carriage of hepatitis B surface antigen (HBsAg) to severe, active variants with progression of fibrosis, formation of liver cirrhosis, and the development of hepatocellular carcinoma (HCC). Despite the successes achieved by the introduction of mass vaccination against hepatitis B, the vertical route of transmission remains an important factor. Every year, 4-5 million children in the world are infected from mothers with CHB[3]. In endemic regions, more than 50% of patients with CHB become infected at birth or in early childhood[4]. The problem of HBV mother-to-child transmission (MTCT) is important because patients infected in early childhood develop CHB in most cases, while the risk of CHB development in patients infected in adulthood is not higher than 20%. Without prophylaxis, MTCT rates vary significantly depending on the mother's hepatitis B e antigen (HBeAg) status: the transmission rate for HBeAg-positive mothers is about 70%-90%, *vs* 10%-40% for HBeAg-negative mothers[5]. In 2016, the WHO set the goal of eliminating viral hepatitis as a major public health threat by 2030[6]. However, this goal cannot be achieved without solving the problem of vertical transmission of HBV. In this context, in order to reduce the HBV MTCT risk, it is important to apply different approaches to the management of pregnancy in women with CHB.

CURRENT LIMITATION ON SCREENING FOR HBSAG IN PREGNANT WOMEN

In most developed and developing countries, all pregnant women are screened for HBsAg. Examining pregnant women only from the so-called risk groups (intravenous drug use, promiscuous sex, work in sex industry, sexual contact with HBsAg carriers) was not enough, since such an examination leaves up to 50% of pregnant women with CHB undetected[7].

Particular attention should be given to women who are diagnosed with CHB for the first time during pregnancy. In these patients, acute hepatitis B has to be excluded. Additional examinations of pregnant women with CHB may differ depending on the region. Table 1 presents the recommendations of the main hepatological communities

Table 1 Examination of pregnant women

	APASL 2016[8]	EASL 2017[9]	AASLD 2018[10]
All pregnant women	Pregnant female (preferably during the first trimester to vaccinate unprotected mothers) should be tested for HBV infection	Screening for HBsAg in the first trimester of pregnancy is strongly recommended	All pregnant women should be screened for HBV infection
Examination of HBsAg-positive women during pregnancy	Maternal HBeAg, HBV DNA status, and ALT level should be checked during pregnancy	ALT, HBV DNA level, and HBsAg level	ALT level, HBV DNA or imaging for HCC surveillance if indicated

APASL: Asia-Pacific Association Society for the Study of the Liver; EASL: European Association for the Study of the Liver; AASLD: American Association for the Study of Liver Diseases; HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen; ALT: Alanine aminotransferase; HCC: Hepatocellular carcinoma.

for the examination of pregnant women with CHB[8-10].

Most recommendations agree that viral load determination is necessary to understand the advisability of antiviral treatment during pregnancy. Recommendations differ as to the timing of therapy initiation and timing of the examination. The viral load determination should be performed no later than week 30 of gestation.

Determination of the HBsAg level during pregnancy is currently prescribed only in the European clinical guidelines for the management of patients with CHB[9]. Meanwhile, available studies indicate a significant correlation between the level of HBsAg during pregnancy and the risk of vertical transmission[11-13]. During pregnancy, HBsAg level is a more stable parameter than viral load, and its measurement is cheaper. Therefore, it can be recommended as a predictor of the vertical transmission of HBV infection, especially in a resource-limited setting. In a pregnant woman with a low HBsAg level, HBV viral load testing is not necessary.

PREVALENCE OF HEPATITIS B IN PREGNANT WOMEN

The prevalence of HBV infection in pregnant women is usually comparable to that in the general population in the same geographic area. In China the prevalence of HBV infection among women of childbearing age is 2%-8%[14,15], while in the United States it is only 0.4%[16].

The prevalence of HBsAg positive patients among pregnant women in several countries is shown in Table 2.

At present, a high HBV prevalence among pregnant women persists in African countries, while the rate of HBsAg-positive pregnant women in Europe and America is low. Even in China, where the prevalence of HBV was very high in the past, a significant reduction in the rate of HBsAg-positive pregnant women is now observed.

COURSE OF CHB AND VERTICAL TRANSMISSION RISK

As agreed by most researchers, there are five phases of the natural course of CHB.

The first phase, called the phase of immune tolerance, usually occurs during perinatal infection and is characterized by a prolonged and low-symptom course, normal serum alanine aminotransferase (ALT) level and minimal changes in liver tissue. As shown in Table 3, patients in this phase of CHB are seropositive for HBeAg and have mostly a high viral load (10^8-10^9 IU/mL HBV DNA)[30,31]. In patients infected in adulthood, the duration of this phase is usually short[32].

The second phase, known as the immunoreactive phase, occurs in patients infected at birth or in early childhood. It starts after two or three decades and is characterized by occasionally increasing ALT values. The anti-HBV immune response results in a moderate (as compared to the first phase) decrease in HBV DNA level. The age of patients when this phase occurs depends on the HBV genotype and varies by geographic region. In Taiwan, 90% of HBeAg seroconversion occurs in patients under the age of 40 years, with genotype B seroconversion occurring earlier than with genotype C[30]. In the European region, no more than 30% of patients remain HBeAg-positive after the age of 40 years[30]. This is important, because the earlier pregnancy occurs, the higher the chances that the woman is in the first phase of CHB, with high viral replication, and, accordingly, a high risk of vertical transmission of HBV

Table 2 Prevalence of hepatitis B surface antigen among pregnant women

Ref.	Country	Years	Number	HBsAg-positive (%)
Kirbak *et al*[17], 2017	Republic of South Sudan	2013-2014	280	11
Fouelifack *et al*[18], 2018	Cameroon	2016	360	9.4
Bittaye *et al*[19], 2019	Gambia	2015	426	9.2
Tanga *et al*[20], 2019	South Western Ethiopia	2017	253	7.9
Kishk *et al*[21], 2020	Egypt	2018-2019	600	5
Fessehaye *et al*[22], 2018	Eritrea	2016	5009	3.2
Sheng *et al*[23], 2018	China	2016	14314	3.1
Cetin *et al*[24], 2018	Turkey	2016	475	2.1
Mishra *et al*[25], 2017	India	2016	3567	1.09
Biondi *et al*[26], 2020	Canada	2012-2016	651745	0.63
Lembo *et al*[27], 2017	Italy	2010-2015	7558	0.5
Ruiz-Extremera *et al*[28], 2020	Spain	2015	21870	0.42
Harris *et al*[29], 2018	United States	2011-2014	870888	0.14

HBsAg: Hepatitis B surface antigen.

Table 3 Clinical features and vertical transmission risk in different phases of chronic hepatitis B

Phase of CHB	ALT	Fibrosis (Metavir score)	HBV DNA level	Markers of HBV-infection	Vertical transmission risk
Phase of immune tolerance	Normal	F0	Very high (10^8-10^9 IU/mL)	HBsAg+; HBeAg+; HBeAb-; HBcorAb+	Very high
Immunoreactive phase	Elevated	F1-F4	High (10^6-10^7 IU/mL)	HBsAg+; HBeAg+/-; HBeAb-/+; HBcorAb+	High
Inactive carriage of HBsAg	Normal	F0	Less than 2000 IU/mL	HBsAg+; HBeAg-; HBeAb+; HBcorAb+	Low
Phase of HBeAg-negative CHB	Elevated	F1-F4	Middle (10^3-10^7 IU/mL)	HBsAg+; HBeAg-; HBeAb+; HBcorAb+	Depends on HBV viral load
Occult CHB	Normal	F1-F4	+/-, HBV DNA in liver+	HBsAg-; HBeAg-; HBeAb-; HBcorAb+/-	Low

CHB: Chronic hepatitis B; ALT: Alanine aminotransferase; HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen; HBeAB: Hepatitis B e antibody; HBcorAb: Hepatitis B core antibody.

infection.

The third phase—the phase of inactive carriage of HBsAg—is characterized by the presence of HBsAg, the absence of HBeAg, and a low (less than 2000 IU/mL) or undetectable HBV viral load. The ALT level is normal in this phase, and no fibrosis progression is observed. Spontaneous HBsAg seroconversion is possible. This phase can continue for decades. The risk of vertical transmission at this stage is low.

The fourth phase, referred to as the HBeAg-negative CHB phase, is characterized by an undulating course, with periodic ALT increases. The HBV viral load can vary significantly, while HBsAg level is a more stable indicator[33]. HBeAg is absent during this phase. There is a gradual progression of fibrosis, and the risk of developing HCC increases. In this phase, the vertical transmission risk depends on HBV viral load.

The fifth phase, called the HBsAg-negative phase or "occult" CHB, is characterized by the disappearance of HBsAg, although the virus continues to replicate in the liver. Clinical symptoms are usually not pronounced, the ALT level remains normal. There is a possibility of CHB reactivation, especially due to immunosuppression, for example a physiological immunosuppression during pregnancy. A few cases of CHB reactivation during pregnancy are reported[34,35]. The vertical transmission risk in

such situations is low.

Management of pregnancy depends on the phase of HBV-infection. Unfortunately, women frequently only learn about their CHB diagnosis during pregnancy. Thus, it is advisable to examine all women for markers of viral hepatitis before pregnancy. During pregnancy, there are limitations for reliably determining the stage of CHB, since several indicators change significantly from the beginning of pregnancy. The level of alpha-fetoprotein increases as early as in the first weeks of pregnancy. Some pathological conditions (toxicosis of the first half of pregnancy, excessive vomiting of pregnant women, *etc.*) can lead to significant changes in cytolytic indicators. In such cases, it is sometimes difficult to determine whether an increase in ALT is caused by these conditions or by CHB activity. Some standard examinations are unreliable during pregnancy. For example, a significant change in circulating blood volume during pregnancy can lead to inaccurate data on liver fibrosis obtained using transient elastography. For this reason, it is preferable to determine the stage of CHB before pregnancy.

Typically, women of childbearing age do not have significant liver fibrosis and cirrhosis. However, due to the increasing age of primiparous women and to the fact that before mass vaccination of newborns against hepatitis B was introduced, one of the main routes of transmission was the vertical route, CHB with advanced fibrosis is not unique. Pregnancy at the stage of liver cirrhosis is also associated with an increased risks of complications for the mother[36].

EFFECT OF PREGNANCY ON THE COURSE OF CHB

In most cases, no exacerbation of CHB occurs during pregnancy, and the cytolytic activity indicators are usually normalized. Nevertheless, a few cases of CHB exacerbation during pregnancy, including development of fulminant liver failure[37,38]. The level of HBV viral load during pregnancy may vary. Cases of CHB reactivation during pregnancy have been known. In one study, in mothers without detectable HBV DNA in the first trimester, HBV DNA was detected in 19.6% of cases in the second trimester and in 30.4% of cases in the third trimester[39]. In another study, the viral load in women with CHB increased during pregnancy and decreased after childbirth[34]. In addition, some studies describe exacerbation of hepatitis in the first months after childbirth[34,40,41]. In the majority of women, the ALT level decreases during pregnancy, but after childbirth there is a significant increase in the cytolytic activity. For example, an increase in ALT level of three times or more was observed in 45% of women within 6 mo after childbirth[34]. Cases of HBeAg seroconversion during pregnancy have also been described in 12.5%-17% of patients[40,41].

Clinical manifestations of CHB in pregnant women are characterized by the predominance of asthenic and dyspeptic syndromes (63%). Hemorrhagic syndrome, such as bleeding gums, was observed in 15% of pregnant women, and hepatomegaly occurred in 10% of cases[42].

PREGNANCY OUTCOMES IN HBV INFECTED WOMEN

The effect of chronic maternal HBV infection on pregnancy outcome has not been well studied. Published works on this topic contradict each other. Some studies show that there is no association between pregnancy outcomes and maternal CHB[43]. Other studies have shown that chronic HBV infection does not result in negative perinatal outcomes, except for lower Apgar scores in newborns[44,45]. However, some studies indicate a high rate of diseases such as fetal distress syndrome, preterm labor and meconium peritonitis among HBV infected women and their newborns[41,46]. A large cohort study carried out in China showed that HBsAg positive pregnant women had a higher risk of gestational diabetes mellitus, postpartum hemorrhage, and intrahepatic cholestasis[44]. A recent study showed a significant correlation between HBV viral load and blood glucose level (fasting blood glucose, 2-h postprandial blood glucose and hemoglobin A1c)[47]. No statistical associations were found between HBsAg positivity and pre-eclampsia, as well as between HBsAg positivity and placenta previa. HBsAg positivity during pregnancy was associated with a higher risk of multiple adverse maternal outcomes.

In a large case-control study in China[48], it was shown that maternal HBsAg carriage was associated with several adverse pregnancy outcomes. In particular, it was correlated with an increased risk of pregnancy-induced hypertension, fetal distress,

cesarean delivery and macrosomia. This study also demonstrated a statistically significant association between high maternal viral load in the second trimester and a high risk of preterm birth. Other previous studies have also reported that maternal HBV infection was associated with an increased risk of preterm birth[49,50], although there are also studies showing the opposite results[51,52].

Some studies indicate a more frequent development of bleeding during childbirth in women with CHB[53]. It was also reported that women with CHB are less likely to have hypertension and pre-eclampsia during pregnancy[51].

CHB THERAPY DURING PREGNANCY

At present, the therapy of CHB cannot yet achieve complete HBV elimination in patients. Therefore, depending on the status of the patient, the goals of CHB therapy may be the following: (1) Suppression of virus replication; (2) Reduction of the inflammatory process in the liver; (3) Reverse the development of fibrosis; (4) Prevention of cirrhosis and HCC development; and (5) Reduction of the HBV vertical transmission risk.

When choosing a therapy, it is necessary to take into account the safety and effectiveness of antiviral drugs, as well as the possibility of drug resistance developing. In women of childbearing age with CHB, antiviral therapy can pursue two main goals: the treatment of women with active CHB and the prevention of vertical transmission (see Table 4). At present, the necessity to treat inactive HBsAg carriers[54] is being discussed, but currently it is recommended only by the Asia-Pacific Association for the Study of the Liver (APASL)[8], while the European Association for the Study of the Liver (EASL)[9] and American Association for the Study of Liver Diseases (AASLD)[10] societies refrain from such recommendations.

A large trial[55] has reported reduced HBV transmission and HBsAg-positivity in infants born to telbivudine or lamivudine treated HBsAg-positive mothers. A systematic review[56] has shown that antiviral therapy of pregnant women with nucleoside analogues (NAs), such as lamivudine, telbivudine or tenofovir, significantly decreases maternal HBV viral load. During pregnancy, tenofovir is the drug of choice, due to its profile of antiviral activity and a low risk of developing resistance. Tenofovir in pregnancy is well tolerated and reduces viral load prior to parturition[57].

NA prophylaxis is also useful in HBeAg-negative women with a high HBV DNA level but normal ALT level[11,55].

The administration of NAs at 28-30 wk of gestation leads to a rapid decrease in the viral load by the time of delivery[58], and, as a consequence, to a significant reduction in vertical transmission risk. However, if the drug intake is discontinued, the viral load quickly returns to its original level. It is reported[58] that a prescription of telbivudine in the third trimester to women with a high viral load leads to an HBV DNA decrease up to an undetectable level at the time of delivery in 33% of patients. In the control group, no such decrease was observed. In the same study, it was shown that there were no cases of vertical transmission in the group of women who received telbivudine in the third trimester, while in the control group, 8% of children 7 mo after delivery were HBsAg-positive. Another large prospective study of 450 HBeAg-positive women with high viral load also showed no vertical transmission in women receiving telbivudine, while in the control group HBsAg was detected in 14.7% of newborns 6 mo after birth[59].

If antiviral therapy was administered in order to prevent MTCT, it is usually discontinued after delivery. However, there is no common opinion how soon after delivery this can be done. As shown in Table 5, according to the AASLD recommendations, the drug can be discontinued soon after delivery; according to EASL — at delivery or within the first 3 mo; while APASL recommends continuing drug intake for 4-12 wk.

HBV PROPHYLAXIS IN NEWBORNS

HBV vaccination reduces the vertical transmission risk from 90% to 21% in HBeAg-positive women and from 30% to 2.6% in HBeAg-negative women[60]. With the addition of hepatitis B immunoglobulin (HBIG), the risk of MTCT is decreased to 6% in HBeAg-positive women and to 1% in HBeAg-negative women[60]. This prophylaxis has to be administered within 12 h after birth (see Table 6).

Table 4 Treatment of pregnant women with chronic hepatitis B

	APASL 2016[8]	EASL 2017[9]	AASLD 2018[10]
Therapy	In pregnant females with chronic HBV infection who need antiviral therapy, tenofovir is the drug of choice for mothers indicated for antiviral treatment during the first through third trimester of pregnancy	Tenofovir is recommended for pregnant women with CHB and advanced fibrosis. Therapy with tenofovir should be continued, and if the woman was receiving other drugs, these other drugs should be replaced with tenofovir	Women who meet standard indications for HBV therapy should be treated. HBV-infected pregnant women with cirrhosis should be managed in high-risk obstetrical practices and treated with tenofovir to prevent decompensation
To prevent vertical transmission	For reduction of risk of mother-to-infant transmission that occurs during the perinatal period, short-term maternal NAs starting from 28 wk to 32 wk of gestation is recommended using either tenofovir or telbuvidine for those mothers with HBV DNA above 6-7 log10 IU/mL. Since, the HBV transmission could occur even with lower maternal HBV DNA level, NAs could be administered after discussion with the patient, even in patients with lower DNA level. The NA could be stopped at birth and when breastfeeding starts, if there is no contraindication to stopping NA	In all pregnant women with high HBV DNA level (> 200000 IU/mL) or HBsAg level > 4 log10 IU/mL, antiviral prophylaxis with tenofovir disoproxil fumarate should start at week 24-28 of gestation and continue for up to 12 wk after delivery	Women without standard indications but who have HBV DNA > 200000 IU/mL in the second trimester should consider treatment to prevent mother-to-child transmission

APASL: Asia-Pacific Association Society for the Study of the Liver; EASL: European Association for the Study of the Liver; AASLD: American Association for the Study of Liver Diseases; HBV: Hepatitis B virus; CHB: Chronic hepatitis B; NA: Nucleoside analogues; HBsAg: Hepatitis B surface antigen.

Table 5 Cessation of nucleoside analogues treatment after delivery

APASL 2016[8]	EASL 2017[9]	AASLD 2018[10]
Cessation of NA therapy (at delivery or 4-12 wk after delivery) is recommended in females without ALT flares and without pre-existing advanced liver fibrosis/cirrhosis. Continuation of NA treatment after delivery may be necessary according to maternal liver disease status	If NA therapy is given as prophylaxis, *i.e.*, only for the prevention of perinatal transmission, its duration is not well defined (stopping at delivery or within the first 3 mo after delivery)	HBV-infected pregnant women who are not on antiviral therapy as well as those who stop antiviral at or early after delivery should be monitored closely for up to 6 mo after delivery for hepatitis flares and seroconversion. Long-term follow-up should be continued to assess need for future therapy

APASL: Asia-Pacific Association Society for the Study of the Liver; EASL: European Association for the Study of the Liver; AASLD: American Association for the Study of Liver Diseases; NA: Nucleoside analogues; ALT: Alanine aminotransferase.

Table 6 Hepatitis B virus prophylaxis in newborns

APASL 2016[8]	EASL 2017[9]	AASLD 2018[10]
HBIG and hepatitis B vaccine can be given to newborns from HBsAg-positive mothers immediately after delivery	The combination of HBIG and vaccination is administered within 12 h of birth	HBIG and HBV vaccine should be administered to the newborn < 12 h after delivery

APASL: Asia-Pacific Association Society for the Study of the Liver; EASL: European Association for the Study of the Liver; AASLD: American Association for the Study of Liver Diseases; HBIG: Hepatitis B immunoglobulin; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus.

The 3-dose vaccine against hepatitis B produces a protective antibody response (anti-HBs ≥ 10 mIU/mL) in approximately 95% of healthy infants[61].

BREASTFEEDING

It is known that in many women infected by HBV, HBsAg can be detected in the breast milk[62]. Moreover, there is evidence that HBV DNA can also be found in breast milk and colostrum[63]. As a result, there are frequent concerns that breastfeeding may facilitate MTCT, although the studies available so far have not confirmed this. No statistically significant differences between breastfed and artificially fed perinatally infected children were detected, and provided a timely vaccination[64-66]. A recent study showed that the frequency of vertical transmission in mothers with similar HBV DNA level is independent of the type of feeding[67]. Thus, HBV infection is not currently considered to be a contraindication to breastfeeding infants receiving HBIG

Table 7 Breastfeeding of newborns

APASL 2016[8]	EASL 2017[9]	AASLD 2018[10]
Breastfeeding is not recommended while the woman is receiving antiviral therapy	Breastfeeding is not contraindicated in women not receiving antiviral therapy and during treatment with tenofovir	Breastfeeding is not prohibited for women with or without antiviral therapy

APASL: Asia-Pacific Association Society for the Study of the Liver; EASL: European Association for the Study of the Liver; AASLD: American Association for the Study of Liver Diseases.

and HBV vaccine. In addition, there are several studies showing that breastfeeding does not affect the child's immune response to vaccination[68]. The current recommendations of major societies are shown in Table 7.

CONCLUSION

Despite the continuously decreasing prevalence of CHB achieved after the introduction of vaccination against hepatitis B, this disease remains a significant public health problem worldwide. In the present study, we summarized the major trends in the management of CHB in pregnant women and provided recommendations for clinical practice necessary to achieve the elimination of hepatitis B as a public health threat, as proposed by the WHO. The most important of these recommendations are: (1) All women have to be screened for HBsAg during pregnancy. Additional examinations of pregnant women with CHB may include maternal HBeAg, HBV viral load, ALT level, and HBsAg level; (2) The management of pregnancy depends on the phase of the HBV infection, which has to be determined before pregnancy; (3) In women of childbearing age with CHB, antiviral therapy can pursue two main goals: treatment of active CHB, and vertical transmission prevention. During pregnancy, tenofovir is the drug of choice in both cases; and (4) A combination of HBIG and vaccine against hepatitis B should be administered within the first 12 h to all infants born to mothers with CHB. In such cases, there are no contraindications to breastfeeding.

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