HBV Infection in Pregnancy

Subjects: Virology

Contributor: Theera Tongsong

Immunological changes during pregnancy such as suppression of Th1 response and induction of Th2 immunity lead to an impaired immune reaction to HBV and stimulate viral activity along with the reduction of CD8 T cells to escape immune detection. The impact of pregnancy on the natural course of chronic HBV infection seems to be minimal, while pregnancy can increase morbidity and mortality in the case of advanced HBV hepatitis or cirrhosis. Importantly, hepatitis flare or alanine aminotransferase (ALT) flare can occur during pregnancy and is more common during the postpartum period due to the interaction between HBV and the immune response. Interestingly, the impact of HBV infection on adverse pregnancy outcomes is more serious than ever thought.

Keywords: hepatitis B virus ; immunological response ; outcomes ; pregnancy

1. Introduction

In the past decades, hepatitis B virus (HBV) infection has been studied extensively. However, the studies of the natural course of the infection during pregnancy are relatively limited, in spite of the fact that maternal-to-child transmission is the main transmission in many parts of the world. Moreover, although immunoprophylaxis to prevent vertical transmission has been widely used, vertical transmission is still a leading cause of high prevalence. In recent decades, immunoprophylaxis failure has been explored. It has been demonstrated that the number of viral copies is associated with prophylaxis failure, resulting in a big change in clinical practice, especially antiviral therapy to lower the transmission rate. The mechanism of transmission is less understood. It might not be as had ever been thought that the main infection is contamination during labor and delivery. Antenatal placental transmission may be a significant cause of failure of prophylaxis after birth. This review updates intrauterine transmission. Additionally, several studies suggest that HBV can increase adverse outcomes, such as intrahepatic cholestasis of pregnancy, gestational diabetes, and preterm birth. Such associations seem to be related to the activity of the HBV. Finally, pregnancy can modify the natural course of HBV infection, especially flare up of hepatitis.

2. Immunological Effect of HBV Infection

2.1. Immune Response to HBV Infection during Pregnancy

A successful pregnancy needs immune adaptation to avoid fetal allograft rejection. The suppression of Th1 response and induction of Th2 immunity leads to an impaired immune reaction to HBV and stimulates viral activity along with the reduction of CD8 T cells to escape immune detection, thereby enhancing vertical transmission since CD8 T cells are the main effector cells responsible for T cell response [1]. Additionally, the pathogenesis during acute HBV infection and viral clearance is mediated by both noncytolytic and cytolytic effector functions of the CD8 T cells [1]. Other than normal immune adaptation during pregnancy, HBV-specific T cell epitopes and responses are important factors.

2.2. Fetal Immune Response

The exposure of the fetus to HBeAg could induce fetal T helper cell tolerance to HBeAg and HBcAg because of the cross reaction [2], increased regulatory T cells, and dysfunctional CD8 T cell. These immune responses were demonstrated in HBsAg-positive newborns with HBV DNA detected at birth; therefore, the fetus may develop immune-tolerance to HBV infection in utero [2][3][4]. Long term exposure to HBV and fetal immune-tolerance could be the causes of immunoprophylaxis failure or persistent infection. However, newborns have a very good response to neonatal vaccination. This may be due to the fact that the main cause of MTCT is peripartum contamination, rather than in utero exposure. Thus the prophylaxis has a good effectiveness, while such prophylaxis may be less effective in cases of placental transmission, occurring long before delivery.

2.3. Effect of Pregnancy on HBV DNA Levels

Some reports suggested that most HBV carriers had stable HBV DNA levels during pregnancy, but increased levels could be found in 5–13% of cases [5][6][7]. However, whether the detection rate of new cases or the incidence of HBV infection is increased or not is still unclear, though theoretically it may be increased because of immune suppression during pregnancy.

2.4. Acute Hepatitis in Pregnancy

Acute hepatitis can occur during any period of pregnancy and postpartum, especially asymptomatic or non-specific clinical presentation such as nausea, vomiting, headache, malaise, etc. Individuals with more severe cases may subsequently develop jaundice or other symptoms of liver failure. HBV, which destroys the liver, does not solely account for the mechanism of acute hepatitis and the cause of liver necrosis, but immunological response also plays a role [8].

2.5. Chronic Hepatitis in Pregnancy

Chronic hepatitis during pregnancy with respect to disease progression is of less concern because of its complicated course of progression and the long period required for it to develop clinical symptoms or complications. Therefore, chronic HBV infection during pregnancy with respect to mother-to-child transmission is the principle concern. However, the phases of chronic HBV infection for each individual should be kept in mind to stay alert for complications.

2.6. Cirrhosis in Pregnancy

Cirrhosis rarely occurs during pregnancy because most cases of cirrhosis occur beyond women's reproductive age [9]. Another reason is that cirrhosis may cause hypothalamic-pituitary dysfunction, and then anovulation and amenorrhea [10] would occur. Importantly, however, severe cirrhotic complications that lead to death are more prevalent in pregnant women with cirrhosis.

2.7. Hepatitis Flare in Pregnancy

Hepatitis flare or ALT flare can occur during pregnancy and the postpartum period due to the interaction between HBV and the immune response. Because of the suppression of cell-mediated immunity to prevent rejection of the fetus, immune response with high replication of HBV can occur during pregnancy and postpartum periods. Baseline characteristics such as HBV DNA levels, baseline ALT, age, HBeAg status, gravida, and parity were not identified as predictors of hepatitis flares [5].

3. HBeAg Seroconversion during Pregnancy and Postpartum

HBeAg seroconversion occurs under immune pressure; immune reactivation, which may lead to elevated ALT and liver inflammation, results in a change in the stage of chronic infection from immune active phase to inactive phase, which shows clinical remission. Compared with non-pregnant women, HBeAg seroconversion in pregnant women increased from 2.2% to 14.3% [11], and 12.5% of seroconversion was observed at 1 year postpartum [12].

4. Pregnancy Outcomes

Other than vertical transmission risk of HBV, pregnancy outcomes among pregnant women with HBV infection are typically very good, though adverse pregnancy outcomes resulting from HBV infection have been reported. Many studies have been conducted to evaluate the association between pregnancy outcomes and HBV infection. Preterm labor, gestational diabetes mellitus, antepartum hemorrhage, preeclampsia, stillbirth, and miscarriage are some of the pregnancy outcomes that have been studied, and some reports found associations between these outcomes and HBV infection [13][14].

However, the mechanisms causing these outcomes have not been extensively evaluated. Some suspected mechanisms were proposed, such as placental inflammation causing placental abruption [15], the role of HBV in induction of insulin resistance resulting in gestational diabetes mellitus [16], and increased immunotolerance or impaired immune function by HBV resulting in a protective effect for preeclampsia [17]. The possible adverse pregnancy outcomes associated with HBV infection may be summarized as presented in **Table 2**.

Table 2. Possible adverse pregnancy outcomes associated with HBV infection.

Adverse Effect	Relative Risk *	Strength of Evidence	Possible Mechanism	Studies (Cohort/Meta-Analysis#)
Miscarriage	↑	Fair	Placental inflammation	Cui et al. 2016 [14]
Preterm birth	↑↑ (in case of HBeAg+)	Fair	Placental inflammation	Tse et al. 2005 [13]; Cui et al. 2016 [14]; Sirilert et al. 2014 [18]; Huang et al. 2014 [19] #; Liu et al. 2017 [20]
Gestational diabetes	↑ (in case of HBeAg+)	Weak	Induction of insulin resistance	Tse et al. 2005 [13]; Sirilert et al. 2014 [18]; Kong et al. 2014 [16] #
Preeclampsia	↓	Fair	Increased immune tolerance by HBV	Huang et al. 2016 [17] #, Zhang et al. 2020 [21]
Placental abruption	↑	Weak	Placental inflammation	Huang et al. 2014 [15] #
Fetal growth restriction	No change	Strong	-	Sirilert et al. 2014 [18] Cui et al. 2016 [14]
Intrahepatic cholestasis	↑↑	Strong	Dysregulation of liver function	Zhang et al. 2020 [21], Jiang et al. 2020 [22] #

* arbitrary estimation by the authors; ↑ (slightly increased); ↑↑ (obviously increased); ↓ (slightly decreased); # Meta-analysis.

5. Mother-to-Child Transmission (MTCT)

Mother-to-child transmission (MTCT) is one of the largest concerns among pregnancies with HBV infection. Acute HBV occurring early in the pregnancy has been associated with a 10% perinatal transmission rate [23]. Transmission rates significantly increase if acute infection occurs at or near the time of delivery, with rates as high as 60% reported [24].

The immunoprophylaxis shortly after birth with an HBV vaccine together with HBIG is very effective in prevention of MTCT. Nevertheless, up to 25–30% of neonates are still infected with HBV because of immunoprophylaxis failure [25].

Transplacental transmission may also play a role in fetal HBV infections. We have demonstrated a significant association between maternal levels of viral replication and placental and fetal infection, suggesting that transplacental infection prior to birth may be a mechanism contributing to the higher rates of newborn prophylaxis failure in women with a high viral load [26].

In prevention of MTCT, in addition to immunoprophylaxis of newborns, antiviral therapy for the mothers with high viral loads can significantly reduce the risk of MTCT. However, though antiviral therapy is now well accepted for the women at high risk of MTCT, safety, timely initial drug administration, and discontinuation need to be elucidated. For example, Bierhoff et al. [27] are conducting a study to evaluate the procedures following early initiation of maternal TDF, before 20 weeks of pregnancy, to determine the effectiveness, safety, and feasibility of this approach in a low-resource setting.

6. Conclusions

Immunological changes induced by pregnancy probably modify the natural course of HBV infection and especially tend to increase hepatitis flare. Growing evidence suggests that placental infection together with hormonal changes caused by pregnancy may be associated with adverse outcomes, especially ICP, GDM, preeclampsia, and preterm birth, etc. Regarding MTCT, immunoprophylaxis failure seems to be associated with high maternal HBV DNA levels and HBeAg positivity. Together with evidence that placental transmission has been consistently demonstrated, in utero infection or placental transmission may also play a role in immunoprophylaxis failure. Antiviral therapy in case of high HBV DNA levels can reduce vertical transmission. Several lines of evidence suggest the effectiveness of antiviral therapy in women with chronic HBV infection with high viral load in addition to hepatitis B immunoglobulin and vaccination for infants.

References

1. Thimme, R.; Wieland, S.; Steiger, C.; Ghrayeb, J.; Reimann, K.A.; Purcell, R.H.; Chisari, F.V. CD8(+) T cells mediate viral clearance and disease pathogenesis during acute hepatitis B virus infection. J. Virol. 2003, 77, 68–76.

2. Milich, D.R.; Jones, J.E.; Hughes, J.L.; Price, J.; Raney, A.K.; McLachlan, A. Is a function of the secreted hepatitis B e antigen to induce immunologic tolerance in utero? Proc. Natl. Acad. Sci. USA 1990, 87, 6599–6603.
3. Trehanpati, N.; Hissar, S.; Shrivastav, S.; Sarin, S.K. Immunological mechanisms of hepatitis B virus persistence in newborns. Indian J. Med Res. 2013, 138, 700–710.
4. Shrivastava, S.; TrehanPati, N.; Patra, S.; Kottilil, S.; Pande, C.; Trivedi, S.S.; Sarin, S.K. Increased regulatory T cells and impaired functions of circulating CD8 T lymphocytes is associated with viral persistence in Hepatitis B virus-positive newborns. J. Viral Hepat. 2013, 20, 582–591.
5. Chang, C.Y.; Aziz, N.; Poongkunran, M.; Javaid, A.; Trinh, H.N.; Lau, D.; Nguyen, M.H. Serum Alanine Aminotransferase and Hepatitis B DNA Flares in Pregnant and Postpartum Women with Chronic Hepatitis, B. Am. J. Gastroenterol. 2016, 111, 1410–1415.
6. Liu, J.; Bi, Y.; Xu, C.; Liu, L.; Xu, B.; Chen, T.; Chen, J.; Pan, M.; Hu, Y.; Zhou, Y.H. Kinetic Changes of Viremia and Viral Antigens of Hepatitis B Virus During and After Pregnancy. Medicine 2015, 94, e2001.
7. Giles, M.; Visvanathan, K.; Lewin, S.; Bowden, S.; Locarnini, S.; Spelman, T.; Sasadeusz, J. Clinical and virological predictors of hepatic flares in pregnant women with chronic hepatitis B. Gut 2015, 64, 1810–1815.
8. Garcia-Romero, C.S.; Guzman, C.; Cervantes, A.; Cerbon, M. Liver disease in pregnancy: Medical aspects and their implications for mother and child. Ann. Hepatol. 2019, 18, 553–562.
9. Fede, G.; Spadaro, L.; Privitera, G.; Tomaselli, T.; Bouloux, P.M.; Purrello, F.; Burroughs, A.K. Hypothalamus-pituitary dysfunction is common in patients with stable cirrhosis and abnormal low dose synacthen test. Dig. Liver Dis. 2015, 47, 1047–1051.
10. Russell, M.A.; Craigo, S.D. Cirrhosis and portal hypertension in pregnancy. Semin. Perinatol. 1998, 22, 156–165.
11. Tan, H.H.; Lui, H.F.; Chow, W.C. Chronic hepatitis B virus (HBV) infection in pregnancy. Hepatol. Int. 2008, 2, 370–375.
12. Lin, H.H.; Wu, W.Y.; Kao, J.H.; Chen, D.S. Hepatitis B post-partum e antigen clearance in hepatitis B carrier mothers: Correlation with viral characteristics. J. Gastroenterol. Hepatol. 2006, 21, 605–609.
13. Tse, K.Y.; Ho, L.F.; Lao, T. The impact of maternal HBsAg carrier status on pregnancy outcomes: A case-control study. J. Hepatol. 2005, 43, 771–775.
14. Cui, A.M.; Cheng, X.Y.; Shao, J.G.; Li, H.B.; Wang, X.L.; Shen, Y.; Mao, L.J.; Zhang, S.; Liu, H.Y.; Zhang, L.; et al. Maternal hepatitis B virus carrier status and pregnancy outcomes: A prospective cohort study. BMC Pregnancy Childbirth 2016, 16, 87.
15. Huang, Q.T.; Chen, J.H.; Zhong, M.; Xu, Y.Y.; Cai, C.X.; Wei, S.S.; Hang, L.L.; Liu, Q.; Yu, Y.H. The risk of placental abruption and placenta previa in pregnant women with chronic hepatitis B viral infection: A systematic review and meta-analysis. Placenta 2014, 35, 539–545.
16. Kong, D.; Liu, H.; Wei, S.; Wang, Y.; Hu, A.; Han, W.; Zhao, N.; Lu, Y.; Zheng, Y. A meta-analysis of the association between gestational diabetes mellitus and chronic hepatitis B infection during pregnancy. BMC Res. Notes 2014, 7, 139.
17. Huang, Q.T.; Chen, J.H.; Zhong, M.; Hang, L.L.; Wei, S.S.; Yu, Y.H. Chronic Hepatitis B Infection is Associated with Decreased Risk of Preeclampsia: A Meta-Analysis of Observational Studies. Cell. Physiol. Biochem. 2016, 38, 1860–1868.
18. Sirilert, S.; Traisrisilp, K.; Sirivatanapa, P.; Tongsong, T. Pregnancy outcomes among chronic carriers of hepatitis B virus. Int. J. Gynecol. Obstet. 2014, 126, 106–110.
19. Huang, Q.T.; Wei, S.S.; Zhong, M.; Hang, L.L.; Xu, Y.Y.; Cai, G.X.; Liu, Q.; Yu, Y.H. Chronic hepatitis B infection and risk of preterm labor: A meta-analysis of observational studies. J. Clin. Virol. 2014, 61, 3–8.
20. Liu, J.; Zhang, S.; Liu, M.; Wang, Q.; Shen, H.; Zhang, Y. Maternal pre-pregnancy infection with hepatitis B virus and the risk of preterm birth: A population-based cohort study. Lancet Glob. Health 2017, 5, e624–e632.
21. Zhang, Y.; Chen, J.; Liao, T.; Chen, S.; Yan, J.; Lin, X. Maternal HBsAg carriers and pregnancy outcomes: A retrospective cohort analysis of 85,190 pregnancies. BMC Pregnancy Childbirth 2020, 20, 724.
22. Jiang, R.; Wang, T.; Yao, Y.; Zhou, F.; Huang, X. Hepatitis B infection and intrahepatic cholestasis of pregnancy: A systematic review and meta-analysis. Medicine 2020, 99, e21416.
23. Jonas, M.M. Hepatitis B and pregnancy: An underestimated issue. Liver Int. 2009, 29 (Suppl. 1), 133–139.
24. Sookoian, S. Liver disease during pregnancy: Acute viral hepatitis. Ann. Hepatol. 2006, 5, 231–236.
25. Hu, Y.; Yu, H. Prevention strategies of mother-to-child transmission of hepatitis B virus (HBV) infection. Pediatric Investig. 2020, 4, 133–137.

26. Sirilert, S.; Khamrin, P.; Kumthip, K.; Malasao, R.; Maneekarn, N.; Tongsong, T. Placental infection of hepatitis B virus among Thai pregnant women: Clinical risk factors and its association with fetal infection. Prenat. Diagn. 2020, 40, 380–386.
27. Bierhoff, M.; Nelson, K.E.; Guo, N.; Jia, Y.; Angkurawaranon, C.; Jittamala, P.; Carrara, V.; Watthanaworawit, W.; Ling, C.; Tongprasert, F.; et al. Prevention of mother-to-child transmission of hepatitis B virus: Protocol for a one-arm, open-label intervention study to estimate the optimal timing of tenofovir in pregnancy. BMJ Open 2020, 10, e038123.