Review Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2025.61.009623

# Pregnancy and Hepatitis B Virus; A Complicated Clinical Challenge Named Anti-HBV Drugs

**Darvishi Mohammad[1], Sha Ali Hamze[2] and Hajilou Fatemeh[3]***

[1]*Associate professor, Infectious diseases and tropical medicine research center (IDTMRC), Department of Aerospace and Subaquatic medicine, AJA university of medicinal sciences, Iran*

[2]*Assistant professor, Department of Aerospace and Subaquatic medicine, AJA university of medicinal sciences, Iran*

[3]*Researcher, Islamic Azad university, Tehran medical branch, Iran*

***Corresponding author:** Hajilou Fatemeh, Researcher, Islamic Azad university, Tehran medical branch, Tehran, Iran

**ARTICLE INFO**

**Received:** April 21, 2025

**Published:** April 29, 2025

**Citation:** Darvishi Mohammad, Sha Ali Hamze and Hajilou Fatemeh. Pregnancy and Hepatitis B Virus; A Complicated Clinical Challenge Named Anti-HBV Drugs. Biomed J Sci & Tech Res 61(4)-2025. BJSTR. MS.ID.009623.

**ABSTRACT**

Hepatitis B virus (HBV) is a small, enveloped, partially double-stranded DNA virus belonging to the Hepadnaviridae family. About 75% of Asian and 12% of African population are chronically infected to HBV. Although this number is lower in Western countries, it is about 2.2 million people in the USA. HBV infection in pregnancy may have several important aspects, many of which are unknown yet. The effects of pregnancy on HBV infection, the potential viral transmission from mother to newborn, its possible prevention through antiviral drugs, and the potential teratogenic effect of these drugs. These factors can make the management of HBV infection complicated in the setting of pregnancy. This review article tries to show the safest drugs that can be used during pregnancy by studying different and related research that has been done in this area recently.

**Keywords:** Pregnancy; Anti-HBV Drugs; Hepatitis B Virus

**Abbreviations:** HBV: Hepatitis B Virus; FDA: Food and Drug Administration; PEG-IFN-α: Pegylated interferon-α; TDF: Tenofovir Disoproxil Fumarate; HBIg: Hepatitis B Immune Globulin; ECS: Elective Cesarean; NVD: Normal Vaginal Delivery

## Introduction

Hepatitis B virus (HBV) is a small, enveloped, partially double-stranded DNA virus belonging to the Hepadnaviridae family. About 75% of Asian and 12% of African population are chronically infected to HBV [1]. Although this number is lower in Western countries, as it is about 2.2 million people in the USA [2]. Not all patients with chronic HBV develop complications, but those with other problems such as liver disease, cirrhosis, and hepatocellular carcinoma develop serious consequences during their lifetimes [3]. More than 750,000 annual deaths are attributed to HBV-related complications around the world. Searching for effective, safe, and available anti-HBV drugs is essential for pregnant patients [4-7]. HBV infection in pregnancy may have several important aspects, many of which are unknown yet. The effects of pregnancy on HBV infection, the potential viral transmission from mother to newborn, its possible prevention through antiviral drugs, and the potential teratogenic effect of these drugs. These factors can make the management of HBV infection complicated in the setting of pregnancy [3,8-10].

## Treatment of HBV During Pregnancy

The decision that whether or not treat HPV in pregnancy and which drug to use, must be taken by considering the risks and benefits of each drug for the mother and fetus. Another aspect is considering the consequences of the treatment on short- and long-term liver disease outcomes of the mother. Also, the most important aspect is using fewer or non-teratogenic drugs [8,11]. The United States Food and Drug Administration (FDA) has announced these drugs as treatments for HBV: PEG-interferon alpha 2a, interferon alpha2b, lamivudine, adefovir, entecavir, telbivudine, and tenofovir [2,8,12-14].

### PEG-Interferon Alpha 2a

Pegylated interferon-α (PEG-IFN-α) is the first choice in the treatment of chronic hepatitis B. IFN-α inhibits HBV replication by decreasing RNA transcription, occurring from covalently closed circular DNA, and because of its effect on DNA, it is not recommended in pregnant women [15].

### Interferon Alpha2b

IFN-α is currently the first choice of antiviral therapy for children with chronic CHB older than one year, while PEG-IFN-α-2a is the recommended treatment for children with CHB older than three years. However, similar to the PEG-interferon aforementioned, it is contraindicated in pregnancy for its effect on DNA. Interferons can be used in breastfeeding for a limited period (48-96 weeks). During the administration of Interferon, the use of a safe contraception method is highly recommended [2,8,11,15].

### Lamivudine

Lamivudine (which is categorized in the FDA C class drugs) has teratogenic or embryocidal effects in animals, but no controlled studies have been done in humans [16]. This drug, which is the first orally approved anti-HBV drug, shows highly toxic effects in the first trimester of rabbit pregnancy. Unfortunately, there is a lack of data about using it in humans [8,9,17].

### Adefovir

Adefovir is an adenine analog reverse transcriptase inhibitor, and due to its nephrotoxicity, its use is limited in pregnant women [18,19].

### Entecavir

Entecavir triphosphate blocks HBV replication by three mechanisms:

(1) Inhibiting the priming of HBV-DNA polymerase,

(2) Inhibiting the reverse transcription of the negative strands of HBV-DNA from the pre-genomic messenger RNA, and

(3) Inhibiting the synthesis of the positive strand of HBV-DNA. Therefore, it is not recommended as treatment of HBV in pregnancy [20,21].

### Telbivudine

Telbivudine (categorized in the FDA B class drugs) showed no teratogenic or embryocidal effects during animal studies. However, there have been no controlled human studies for animal studies that may indicate a risk [22,23].

### Tenofovir

Tenofovir (categorized in the FDA B class drugs) has a high power with a high genetic barrier to resistance [11,24].

## Hepatitis B in Pregnancy

Lamivudine and tenofovir, with the most in vivo experience in the first trimester, may be safe for pregnant patients. [8,22]. Deciding what anti-HBV therapy to administer in pregnant women has its difficulties, especially with multiple parameters that must be considered age, stage of disease, comorbidity, viral load, genotype, power of the agent, genetic barrier to resistance, etc., and must be studied case by case [4,8]. For women planning to have a child and who are untreated, it is recommended to postpone therapy until the child is born [2,8]. In pregnant women who use treatments in advance and with significant fibrosis, therapy should be continued to reduce the risk of decompensation of liver disease. This would affect the health of the fetus, and it is preferable to replace it with a safe drug during pregnancy [5,8]. WHO guidelines recommend antiviral prophylaxis in preventing mother-to-child transmission in infants born to HBV infected women regardless of the antiviral used. Tenofovir disoproxil fumarate (TDF) has a high genetic barrier to resistance and is the medicine of choice for both prevention of mother to child transmissions and treatment of chronic hepatitis B infection. There was a low risk of maternal HBV flare after TDF discontinuation in the studies that reported on this outcome. The Guidelines Development Group also determined a HBV DNA viral load threshold of ≥5.3 log10 IU/mL (≥200,000 IU/mL) at which pregnant women are eligible to receive tenofovir prophylaxis.

Pregnant woman with a viral load above this level may transmit HBV to their infant even when the infant receives the timely birth dose vaccine, Hepatitis B immune globulin (HBIg) HBIG and completes the hepatitis vaccine series [14]. Although HBV DNA quantification is the reference method to determine eligibility for tenofovir prophylaxis, the use of HBeAg was recommended as an acceptable alternative test in settings where access to HBV DNA quantification is limited. This was based on a further systematic review that showed the overall sensitivity and specificity of HBeAg for diagnosis of high HBV viral load (defined as ≥5.3 log10 IU/mL) was 88.2% (95% CI: 83.9–91.5) and 92.6% (95% CI: 90–94.5) respectively. Overall, HBeAg has a high sensitivity but lower specificity for predicting the risk of mother-to-child transmission [14]. In Iran, although there are not enough data supporting using Tenofovir, guidelines suggest using Tenofovir in pregnant women in contrast to other drugs. Interferon is contraindicated in these patients [25].

## Prevention of Mother to Child HBV Transmission with Antiviral Drugs

According to studies, there is no safe treatment to prevent perinatal transmission in women who are HBsAg-positive with high viremia in the third trimester [8,11]. In a study published in 2003, eight women with HBV DNA levels greater than 109 copies/mL were given 150 mg of lamivudine daily during the last month of pregnancy. Newborns received passive and active immunization, and only one of them became infected, compared to 7of 25 (28%) cases of transmis-

sion in a matched historical control population [8,26]. A randomized, double-blind, placebo-controlled trial done with 150 HBs Ag positive highly viremic pregnant women evaluated whether lamivudine administered from the 32nd week of gestation to the 4th week post-partum prevented HBV transmission to newborns who received standard prophylaxis with HBIG and vaccination. All but one woman were HBe Ag positive. At 1 year old, 18% of babies from lamivudine-treated mothers were HBs Ag positive, versus 39% in the placebo-treated group (P=0.014). Based on these results, Xu et al recommended treatment for women with high viral loads in the third trimester [23]. However, these data should be interpreted with caution due to a high dropout rate (13% in the lamivudine group versus 31% in the placebo group). There were no safety concerns in the lamivudine-treated mothers and their infants [8]. A recent meta-analysis of 10 randomized controlled trials for a total of 951 HBV positive mothers evaluated the efficacy of lamivudine in reducing in-utero transmission of HBV [24].

The results prove the safety of lamivudine and its efficacy in preventing HBV intrauterine infection and mother-to-child transmission. However, the limitation of meta-analysis is the different quality of the studies included and the heterogeneity of the cut-off values for high viral load that prompted therapy [8,27]. A non-randomized, controlled trial that included 190 HBs Ag positive, HBe Ag positive pregnant women with high viremia (>106 copies/mL) evaluated the efficacy and safety of telbivudine versus placebo. In both groups, newborns were treated with standard active/passive prophylaxis within 24 hours of birth. Telbivudine was given to mothers from 20 to 32 weeks before delivery and was continued for 4 weeks after delivery in the case of inactive disease and 28 weeks in the case of active chronic hepatitis. At birth, a meaningful reduction of HBs Ag positivity rate was observed in babies born from telbivudine-treated mothers compared to the control group (6.3% vs 30.4%). Twenty-eight weeks after birth, the rate of HBs Ag or HBV DNA positivity was significantly reduced in babies born from telbivudine-treated mothers versus placebo-treated ones (2% vs 13%). Postpartum alanine aminotransferase (ALT) flaring occurred in 7.5% of telbivudine-treated women and 18.5% of placebo-treated women. No safety concerns were observed for mothers or children in either group. No cases of severe hepatitis were observed in women who discontinued telbivudine at week four postpartum.

These data confirm the need for antiviral therapy in HBe Ag positive pregnant women with high viremia (> 106 copies/mL) and the efficacy and safety of telbivudine in this setting [8,28]. Now, there was little data about the efficacy of tenofovir in pregnant women. Some information regarding the toxicity of tenofovir comes from studies on animals, such as pregnant rhesus monkeys, which found a reduction of circulating insulin-like growth factor in newborns and severe growth reduction in approximately 25% of the infant monkeys within two months of maternal treatment [8]. However, tenofovir is expected to be at least as effective as lamivudine in reducing perinatal transmission; it is an attractive agent to consider in the third trimester [8,9].

## Management of HBV in Every Trimester of Pregnancy

Every pregnant woman should be screened for HBV infection in the first trimester. If they are negative, they don't have to be vaccinated during pregnancy, although vaccination is mandatory for all pregnant women with high-risk behavior. Their children will be vaccinated for hepatitis B together with other routine vaccines. If the test of a pregnant woman is positive in early pregnancy, it's necessary to assess the severity and progression of the disease. When their disease is very active (significantly elevated ALT with a high viral load), or cirrhosis is suspected, treatment should be administered at each gestational age. In pregnant patients with inactive disease (low ALT and low viral load), treatment is not necessary and continued surveillance is suggested because of the risk of a flare of hepatitis B later in pregnancy and for several months postpartum [2,8,11].

## Elective Cesarean (ECS) Versus Normal Vaginal Delivery (NVD) in Preventing HBV Transmission

In a meta-analysis that studied 789 pregnant women with HBV infection, ECS considerably reduced the rate of HBV maternal transmission (ECS: 10.5%; vaginal delivery: 28.0%) (Relative risk: 0.41, 95% CI 0.28 to 0.60, P.value < 0.000, 001). Currently, the role of ECS in preventing mother-to-child transmission of HBV infection is ambiguous, and there is no convincing evidence that ECS reduces the rate of mother-to-child transmission of HBV compared with NVD [8,14].

## Breastfeeding by HBV-Infected Mothers

Although the high vertical transmission rates confused the true rate of acquisition from breastfeeding, the current guidelines state that breastfeeding is not contraindicated in HBV-infected mothers who are not on antiviral therapy and for infants who receive immunoprophylaxis [29]. For mothers on antiviral therapy with lamivudine or tenofovir, breastfeeding is not recommended due to few data available about the safety of antiviral exposure during breastfeeding [8,11,30].

## Conclusion

The decision whether or not to treat HBV infection in pregnancy and drug choice must be taken by considering the risks and benefits of each drug for the mother and fetus. It seems that, among drugs that the FDA has announced (PEG-interferon alpha 2a, interferon alpha 2b, lamivudine, adefovir, entecavir, telbivudine, and tenofovir), lamivudine and tenofovir (with the most in vivo experience in the first trimester) are safe to be used.

## References


1. Lavanchy D (2004) Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. Journal of viral hepatitis 11(2): 97-107.
2. Tran TT (2009) Management of hepatitis B in pregnancy: weighing the options. Cleveland Clinic journal of medicine 76(Suppl 3): S25-S29.
3. Nguyen G, Garcia RT, Nguyen N, Trinh H, Keeffe EB, et al. (2009) Clinical course of hepatitis B virus infection during pregnancy. Alimentary pharmacology & therapeutics 29(7): 755-764.
4. Jonas MM (2009) Hepatitis B and pregnancy: an underestimated issue. Liver international: official journal of the International Association for the Study of the Liver 29(Suppl 1): 133-139.
5. Lim E, Mouyis M, MacKillop L (2021) Liver diseases in pregnancy. Clinical medicine (London, England) 21(5): e441-e445.
6. Russell MA, Craigo SD (1998) Cirrhosis and portal hypertension in pregnancy. Seminars in Perinatology 22(2): 156-165.
7. ter Borg MJ, Leemans WF, de Man RA, Janssen HL (2008) Exacerbation of chronic hepatitis B infection after delivery. Journal of viral hepatitis 15(1): 37-41.
8. Borgia G, Carleo MA, Gaeta GB, Gentile I (2012) Hepatitis B in pregnancy. World journal of gastroenterology 18(34): 4677-4683.
9. Wright TL (2006) Introduction to Chronic Hepatitis B Infection. Official journal of the American College of Gastroenterology 101(Suppl 1): S1-S6.
10. Maynard JE (1990) Hepatitis B: global importance and need for control. Vaccine 8: S18-S20.
11. Bzowej NH (2010) Hepatitis B Therapy in Pregnancy. Current hepatitis reports 9(4): 197-204.
12. Petersen J (2011) HBV treatment and pregnancy. Journal of Hepatology 55(6): 1171-1173.
13. Degli Esposti S, Shah D (2011) Hepatitis B in Pregnancy: Challenges and Treatment. Gastroenterology Clinics 40(2): 355-372.
14. Patton H, Tran TT (2014) Management of hepatitis B during pregnancy. Nature Reviews Gastroenterology & Hepatology 11(7): 402-409.
15. Hajilou F, Youeseflee P, Pashaei M, Bagheri K, Bagheri B (2022) Review on Interferon beta: from cells to clinical usage. Koomesh 24(1): 26-37.
16. Benhamou Y, Katlama C, Lunel F, Coutellier A, Dohin E, et al. (1996) Effects of Lamivudine on Replication of Hepatitis B Virus in HIV-Infected Men. Annals of Internal Medicine 125(9): 705-712.
17. Lisotti A, Azzaroli F, Buonfiglioli F, Montagnani M, Alessandrelli F, et al. (2008) Lamivudine treatment for severe acute HBV hepatitis. International journal of medical sciences 5(6): 309-312.
18. Marcellin P, Asselah T (2005) Resistance to adefovir: A new challenge in the treatment of chronic hepatitis B. Journal of Hepatology 43(6): 920-923.
19. Dusheiko G (2003) Adefovir dipivoxil for the treatment of HBeAg-positive chronic hepatitis B: a review of the major clinical studies. Journal of Hepatology 39(Suppl 1): S116-S123.
20. Matthews SJ (2006) Entecavir for the treatment of chronic hepatitis B virus infection. Clinical Therapeutics 28(2): 184-203.
21. Langley David R, Walsh Ann W, Baldick Carl J, Eggers Betsy J, Rose Ronald E, et al. (2007) Inhibition of Hepatitis B Virus Polymerase by Entecavir. Journal of Virology 81(8): 3992-4001.
22. Terrault NA, Jacobson IM (2007) Treating chronic hepatitis B infection in patients who are pregnant or are undergoing immunosuppressive chemotherapy. Seminars in liver disease 27(Suppl 1): 18-24.
23. Amarapurkar DN (2007) Telbivudine: a new treatment for chronic hepatitis B. World journal of gastroenterology 13(46): 6150-6155.
24. Agarwal K, Brunetto M, Seto WK, Lim Y S, Fung S, et al. (2018) 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. Journal of Hepatology 68(4): 672-681.
25. Badfar G, Shohani M, Nasirkandy MP, Mansouri A, Abangah G, et al. (2018) Epidemiology of hepatitis B in pregnant Iranian women: a systematic review and meta-analysis. Archives of Virology 163(2): 319-330.
26. van Zonneveld M, van Nunen AB, Niesters HG, de Man RA, Schalm SW, et al. (2003) Lamivudine treatment during pregnancy to prevent perinatal transmission of hepatitis B virus infection. Journal of viral hepatitis 10(4): 294-297.
27. Shi Z, Yang Y, Ma L, Li X, Schreiber A (2010) Lamivudine in late pregnancy to interrupt in utero transmission of hepatitis B virus: a systematic review and meta-analysis. Obstetrics and gynecology 116(1): 147-159.
28. Han GR, Cao MK, Zhao W, Jiang HX, Wang CM, et al. (2011) A prospective and open-label study for the efficacy and safety of telbivudine in pregnancy for the prevention of perinatal transmission of hepatitis B virus infection. Journal of hepatology 55(6): 1215-1221.
29. Lok AS, McMahon BJ (2009) Chronic hepatitis B: update 2009. Hepatology Baltimore, Md 50(3): 661-662.
30. Petrova M, Kamburov V (2010) Breastfeeding and chronic HBV infection: clinical and social implications. World journal of gastroenterology 16(40): 5042-5046.


**ISSN: 2574-1241**

DOI: 10.26717/BJSTR.2025.61.009623

**Hajilou Fatemeh.** Biomed J Sci & Tech Res