Hepatitis Monthly 2008; 8(1): 71-74

GUIDELINE AND CLINICAL ALGORHYTHM

The Strategy of Antivirus Treatment in Reproductive Women Infected with Hepatitis B Virus

CAI Hao-Dong*, LIU Min

Beijing Ditan Hospital, Beijing 100011, China

Chronic hepatitis B is caused by persistent infection with hepatitis B virus (HBV). In the last decade, great progress has been made in the treatment of chronic hepatitis B. Prognosis of chronic hepatitis B has been improved significantly because of the clinical application of nucleoside/nucleotide analogues, such as lamivudine, adefovir dipivoxil, and entecavir. More and more importance of antivirus treatment has been realized. But the physicians are being puzzled by the problems of antivirus treatment in the reproductive women infected with HBV. According to the studies of antiviral drug safety and clinical experiences in treating pregnant women in recent years, we introduce the strategies of antivirus treatment in different periods of reproductive women infected with HBV.

1. Problems of antivirus treatment in the reproductive women infected with HBV

The incidence rates of pregnancy-induced hypertension syndrome, postpartum hemorrhage, infection of incisional wound, intrauterine infection, HBV vertical infection and perinatal mortality rate increase significantly in the women infected with HBV, especially in those who develop an immune clearance period with abnormal liver function [1, 2], than in healthy women. In addition, the rate of mother-to-child transmission is highly correlated with the level of maternal HBV replication [3]. If the mother's serum is positive for HBV-DNA, the transmission rate is up to 90%; whereas, if negative, the transmission rate is only 10-30%. When HBV-DNA levels in pregnant women are $<1\times10^6$ copies/ml, the risk of mother-to-child transmission of HBV decreases by 30%. If HBV replication could be inhibited effectively, the mother-to-child transmission would be interrupted significantly. Therefore, antivirus treatment is necessary in these women but antiviral effect of interferon is limited.

Since nucleoside/nucleotide analogues treatment is long term and only 20% of HBeAg positive patients achieve HBeAg seroconversion by short-term treatment, and 12% of the patients keep sustained response of HBV inhibition after drug withdrawal [4], reproductive women receiving antiviral therapy may get pregnant during treatment. Therefore, the physicians are concerned about the type of antiviral drugs that should be prescribed in reproductive women infected with HBV, whether the treatment should be discontinued during pregnancy and if the drug is safe for the mother and the baby.

2. The safety of antiviral drugs in women during pregnancy and lactation

Nowadays, there are two main categories of antiviral drugs for HBV: interferon and nucleoside/nucleotide analogues. Six antiviral agents (standard interferon, peginterferon, lamivudine, telbivudine, adefovir dipivoxil, and entecavir) have been approved for the treatment of chronic hepatitis B in our country and several drugs, such as tenofovir and emtricitabine are still in the process of research. Medications are classified into five categories according to the safety during pregnancy by U.S. FDA [5]. Category A (controlled studies show no risk and the possibility of fetal harm appears remote); B (animal studies show no risk, but human

* Correspondence:
CAI Hao-Dong, Beijing Ditan Hospital, Beijing 100011, China.

Tel: +86 1064290168
Fax: +86 1064279947

E-mail: chddt@163.com

Received: 17 Nov 2007 Revised: 24 Feb 2008
Accepted: 19 Apr 2008

Hep Mon 2008; 8 (1): 71-74

studies have not been done or vice versa); C (animal data show teratogenic effects but no controlled studies done in humans); D (human fetal risk exists but benefit outweighs risks); or X (fetal risk outweighs benefit and prohibited use in pregnancy).

Currently, lamivudine, telbivudine, emtricitabine, and tenofovir are classified as category B in the seminar on chronic hepatitis B therapy in American [5], indicating that they demonstrate no evidence of teratogenicity in animal studies but have not been adequately evaluated in humans and ongoing registries include few instances of pregnancy during therapy to provide reliable guidance. These agents could be used if the potential benefit of treating during pregnancy is believed to outweigh potential risks to mother or fetus. Many studies regarding the safety of lamivudine in pregnant women are available at present. Initial studies discovered that lamivudine could pass placenta and be secreted in milk as well. However, clearance rate of lamivudine in neonates was only half of that in other children [6-8].

Afterwards, many animal studies demonstrated that there were no teratogenic effects to the immature mice which were exposed to lamivudine at different doses in uterus for a long time, even at high doses, and neurotoxicity of lamivudine was obviously lower than zidovudine. Behavior of immature mice would be influenced after birth if exposed to high doses of lamivudine (500 mg/kg) in uterus [9-11]. Lamivudine was safe to the pregnant mice and their offspring, and could effectively reduce the serum HBV-DNA levels of mother mice [12], which may be because lamivudine belongs to L-nucleoside analog and there is no effect on human nuclear acid [6]. The data in pregnant women infected with HIV has not shown any serious adverse reactions and impacts on reproductive process, embryotoxicity and neonatal development related to lamivudine [13-17].

Global studies [18-23] have demonstrated that lamivudine is safe and effective in interrupting mother to child HBV transmission at late trimester of pregnancy. In addition, three reports [24-26] showed that the women who were unable to stop the treatment or volunteered to continue the therapy when they became pregnant on lamivudine treatment were treated effectively. The mother to child HBV transmission was interrupted and no obvious impacts on infants were observed [27].

Telbivudine is a new drug commercially available, and no related reports in animal experiments and treatment during pregnancy could be searched. Tenofovir is not recommended in pregnant women and while mothers are breast feeding because it might affect bone density. Entecavir and adefovir are classified as category C, in that embryo and fetal toxicities have been observed in animals, but these reproduction studies are not always predictive of human response. So they should be used cautiously during gestation. Interferon and peginterferon are contraindicated during pregnancy largely because of their known anti-proliferative effects. In the event of pregnancy, interferon, and peginterferon should be discontinued [5].

3. The strategy of antivirus treatment in reproductive women infected with HBV

It is well known that the treatment of chronic hepatitis B is refractory and long term. According to the above study results and the features of antiviral drugs, different strategies of antivirus treatment can be adopted in reproductive women infected with chronic HBV (Fig 1).

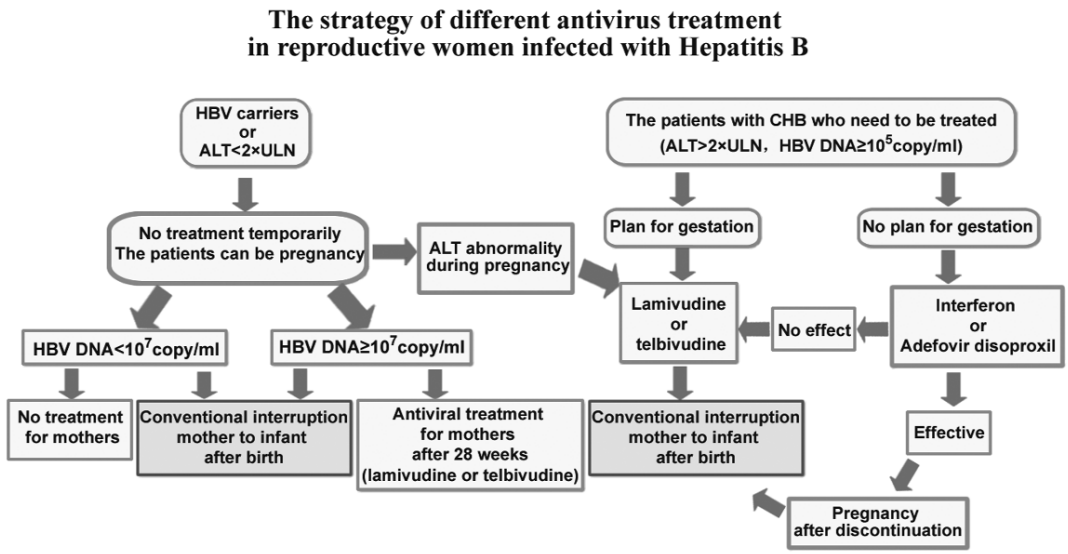

Figure 1. Different antivirus treatment strategies in reproductive women with chronic hepatitis B.

a. The strategy of antivirus therapy before gestation in reproductive women with HBV carrier status

Pregnancy should be considered in reproductive women >18 years old before initiating antivirus treatment. Generally, treatment is not recommended for the patients with normal liver function because the therapeutic effects on HBV carrier state are little. Liver protection treatment is recommended in the patients with mild abnormal liver function (ALT <2×ULN) so as to avoid doing harm to mother and infant if the drug is discontinued suddenly during pregnancy or the fetus is exposed to the antiviral drug.

b. The strategy of antivirus therapy during pregnancy in reproductive women with HBV carrier status

In order to interrupt HBV transmission from mother to infant in women with HBV DNA level $\geq 10^7$ copies/ml, treatment with lamivudine 100 mg once daily or telbivudine 600 mg once daily after 28 weeks of gestation could be adopted with informed consent from the patients and their families. The treatment could be discontinued one month after delivery or continued for a period. But the patients and their families should be informed that viral rebound may occur after discontinuation, therapeutic effects of continuing treatment on HBV carriers are little and drug resistance may develop. Breastfeeding should be prohibited during treatment.

c. The strategy of antivirus therapy before pregnancy in reproductive women with chronic hepatitis B

For reproductive women with chronic hepatitis B (ALT >2×ULN and HBV-DNA $\geq 10^5$ copies/ml) who have no plan to be pregnant in the near future and need to be treated interferon or adefovir dipivoxil is recommended, but not lamivudine, telbivudine and entecavir. The course of interferon treatment is short and the viral rebound after withdrawal is not common. So if the patients achieve HBeAg seroconversion, their medication could be discontinued and they can be prepared for pregnancy. Adefovir dipivoxil belongs to category C of drug safety during pregnancy. Its use is not recommended during pregnancy because of the potential renal toxicity. However, 1/4 of patients may develop HBeAg seroconversion, and their treatment could be discontinued and they can become pregnant. In addition, there are no cross-resistance to drugs between interferon, adefovir dipivoxil and lamivudine, telbivudine. If the treatment with interferon or adefovir dipivoxil is not successful, the patients could switch to lamivudine or telbivudine and the impacts on pregnancy should be considered if the patients wish to become pregnant.

Lamivudine and telbivudine belong to category B of drug safety during pregnancy and are not adopted temporarily because they could be an option of treatment during pregnancy. If lamivudine or telbivudine treatment is initiated too early, drug resistance would develop and probably no drugs could be selected at that time. Entecavir belongs to category C of drug safety during pregnancy and may be of risk during gestation. Entecavir can suppress viral replication effectively, but its rate of HBeAg seroconversion is low, so most patients need long-term treatment. Meanwhile, the mechanism of drug resistance to entecavir is similar to lamivudine or telbivudine. It is confirmed that the drug resistance to lamivudine can be induced by entecavir in the patients with HIV/HBV co-infection [28]. It is almost impossible to switch to lamivudine or telbivudine during pregnancy and entecavir may be harmful, so it is not recommended to be used before gestation.

Reproductive women with chronic hepatitis B (ALT >2×ULN, while HBV-DNA $\geq 10^5$ copies/ml) who need to be treated: if they have planned to be pregnant in the near future, lamivudine or telbivudine treatment could be considered after fully discussion with the patients and their families. Currently, the women infected with HIV are recommended to be treated with lamivudine and zidovudine during gestation according to experiences in clinical practice. Therefore, if the women with chronic hepatitis B become pregnant or have plans to become pregnant during treatment, lamivudine is recommended to be used or switch to [5]. Gestation could be considered after achieving antiviral therapeutic effects (decreased HBV-DNA level and normalized ALT) with treatment for 3-6 months.

d. The strategy of antivirus therapy during gestation in reproductive women with chronic hepatitis B

The reproductive women with chronic hepatitis B who develop abnormal liver function after gestation (ALT ≥2×ULN and HBV-DNA $\geq 10^5$ copies/ml, or ≥104 copies/ml in HBeAg negative patients) need to be treated. Lamivudine or telbivudine treatment could be considered after fully discussion with patients and their families but ALT of the patients should be monitored closely. Some patients may develop strong immune responses at the same time of viral suppression at early stages of treatment. In addition, liver is overburdened during pregnancy so liver function is deteriorated rapidly and the lives of mother and child are threatened.

More and more literature has been started to investigate the safety of these drugs in pregnant women, since the scientists from all over the world pay more attention to the antiviral treatment in pregnant women. The strategies of antivirus treatment in reproductive women introduced in this article are just for your reference. We hope that women infected with HBV who account for 1/3 of chronic HBV infected patients could receive correct therapy and mother to child transmission of HBV could be interrupted as much as possible.

References

1. Xiao Y. Issues in pregnant women infected with chronic hepatitis B. *Modern Journal of Integrated Traditional Chinese and Western Medicine* 2007; **16**: 207-8.
2. Zhao SH, Han LY, Zhang LH, Sun YX. Influence to pregnancy and their infants and protective measure in hepatitis B virus carriers. *Journal of Norman Bethune University of Medical Sciences* 2000; **26**: 75-6.
3. Ranger-Rogez S, Alain S, Denis F. Hepatitis viruses: mother to child transmission (in French). *Pathol Biol* 2002; **50**: 568-75.
4. Marcellin P, Asselah T, Boyer N. Treatment of chronic hepatitis B. *J Viral Hepat* 2005; **12**: 333-45.
5. Hoofnagle JH, Doo E, Liang TJ, Fleischer R, Lok AS. Management of hepatitis B: summary of a clinical research workshop. *Hepatology* 2007; **45**: 1056-75.
6. Johnson MA, Moore KH, Yuen GJ, Bye A, Pakes GE. Clinical pharmacokinetics of lamivudine. *Clin Pharmacokinet* 1999; **36**: 41-66.
7. Moodley J, Moodley D, Pillay K, Coovadia H, Saba J, van Leeuwen R, *et al.* Pharmacokinetics and antiretroviral activity of lamivudine alone or when coadministered with zidovudine in human immunodeficiency virus type 1-infected pregnant women and their offspring. *J Infect Dis* 1998; **178**: 1327-33.
8. Mandelbrot L, Peytavin G, Firtion G, Farinotti R. Maternal-fetal transfer and amniotic fluid accumulation of lamivudine in human immunodeficiency virus-infected pregnant women. *Am J Obstet Gynecol* 2001; **184**: 153-8.
9. Venerosi A, Valanzano A, Alleva E, Calamandrei G. Prenatal exposure to anti-HIV drugs: neurobehavioral effects of zidovudine (AZT) + lamivudine (3TC) treatment in mice. *Teratology* 2001; **63**: 26-37.
10. Ricceri L, Venerosi A, Valanzano A, Sorace A, Alleva E. Prenatal AZT or 3TC and mouse development of locomotor activity and hot-plate responding upon administration of the GABA(A) receptor agonist muscimol. *Psychopharmacology* 2001; **153**: 434-42.
11. Calamandrei G, Venerosi A, Branchi I, Valanzano A, Puopolo M, Alleva E. Neurobehavioral effects of prenatal lamivudine (3TC) exposure in preweaning mice. *Neurotoxicol Teratol* 1999; **21**: 365-73.
12. Li D, Xu DZ, Choi BC, Men K, Zhang JX, Lei XY, *et al.* Preliminary study on the efficacy and safety of lamivudine and interferon alpha therapy in decreasing serum HBV DNA level in HBV positive transgenic mice during pregnancy. *J Med Virol* 2005; **76**: 203-7.
13. Divi RL, Walker VE, Wade NA, Nagashima K, Seilkop SK, Adams ME, *et al.* Mitochondrial damage and DNA depletion in cord blood and umbilical cord from infants exposed in utero to Combivir. *AIDS* 2004; **18**: 1013-21.
14. Poblano A, Figueroa L, Figueroa-Damian R, Schnaas L. Effects of prenatal exposure to Zidovudine and Lamivudine on brainstem auditory evoked potentials in infants from HIV-infected women. *Proc West Pharmacol Soc* 2004; **47**: 46-9.
15. El Beitune P, Duarte G, Foss MC, Montenegro RM, Jr., Quintana SM, Figueiro-Filho EA, *et al.* Effect of maternal use of antiretroviral agents on serum insulin levels of the newborn infant. *Diabetes Care* 2005; **28**: 856-9.
16. Blanche S, Tardieu M, Rustin P, Slama A, Barret B, Firtion G, *et al.* Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. *Lancet* 1999; **354**: 1084-9.
17. Watts DH, Covington DL, Beckerman K, Garcia P, Scheuerle A, Dominguez K, *et al.* Assessing the risk of birth defects associated with antiretroviral exposure during pregnancy. *Am J Obstet Gynecol* 2004; **191**: 985-92.
18. van Zonneveld M, van Nunen AB, Niesters HG, de Man RA, Schalm SW, Janssen HL. Lamivudine treatment during pregnancy to prevent perinatal transmission of hepatitis B virus infection. *J Viral Hepat* 2003; **10**: 294-7.
19. Li XM, Yang YB, Hou HY, Shi ZJ, Shen HM, Teng BQ, *et al.* Interruption of HBV intrauterine transmission: a clinical study. *World J Gastroenterol* 2003; **9**: 1501-3.
20. Xu WM, Cui YT, Wang L, Yang H, Liang ZQ, Li XM, *et al.* Efficiacy and safety of lamivudine in late pregnancy for the prevention of mother to child transmission of hepatitis B virus; a multicenter, randomised, double-blind, placebo-controlled study. *Hepatology* 2004; **40**: 272A-3A.
21. Shi MF, Li XM, He J, Yang YB, Hou HY, Zhuang YL, *et al.* Research on interruption of hepatitis B virus intrauterine infection by lamivudine. *Clinical Medicine of China* 2005; **21**: 77-8.
22. Wang TM, Qiu B, Chen Y, Wu XL. Clinical research on interruption of hepatitis B virus mother-to-child transmission by lamivudine. *Chinese Journal of Birth Health & Heredity* 2005; **13**: 68-9.
23. Han ZH, Chen YH, Li LW, Sun XW, Sun YG, Zhao H, *et al.* Effect and safety on interruption of hepatitis B virus mother-to-child transmission by lamivudine. *Chinese Journal of Internal Medicine* 2005; **44**: 378.
24. Loreno M, Bo P, Senzolo M, Cillo U, Naoumov N, Burra P. Successful pregnancy in a liver transplant recipient treated with lamivudine for de novo hepatitis B in the graft. *Transpl Int* 2005; **17**: 730-4.
25. Su GG, Pan KH, Zhao NF, Fang SH, Yang DH, Zhou Y. Efficacy and safety of lamivudine treatment for chronic hepatitis B in pregnancy. *World J Gastroenterol* 2004; **10**: 910-2.
26. Chi XL, Xiao HM. Gestation during Heptodin treatment for chronic hepatitis B: a case report. *New Journal of Traditional Chinese Medicine* 2006; **38**: 89-90.
27. Cai HD, Wang L, Liu M. The safety and effect of lamivudine in treating pregnant women infected with hepatitis B virus (in Chinese). *Zhonghua Gan Zang Bing Za Zhi* 2006; **14**: 151-3.
28. McMahon MA, Jilek BL, Brennan TP, Shen L, Zhou Y, Wind-Rotolo M, *et al.* The HBV drug entecavir-effects on HIV-1 replication and resistance. *N Engl J Med* 2007; **356**: 2614-21.