Efficacy and safety of lamivudine treatment for chronic hepatitis B in pregnancy

Guan-Guan Su, Kong-Han Pan, Nian-Feng Zhao, Su-Hua Fang, Dan-Hong Yang, Yong Zhou

AIM: To evaluate the efficacy and safety of lamivudine treatment of chronic hepatitis B disease in pregnancy.

METHODS: The study group was comprised of 38 chronic HBV patients who were diagnosed pregnant during lamivudine treatment and voluntary to continue the same therapy. The control group was from documented patient data in the literatures. We compared the following parameters with those of a control group: anti-HBV efficacy, complications of pregnancy (abortion, preterm birth, neonatal asphyxia, fetal death, and congenital anomaly), incidence of HBV-positive babies and developmental anomalies in pregnant women treated with lamivudine.

RESULTS: The blocking rate of lamivudine treatment was significantly higher than that of active vaccine immunization for babies with double-positive (HBsAg/HBeAg) mothers with 30-30-10 μg doses of vaccine (74.07%) and with 30-20-10 μg (64.87%). The natural vertical HBV transmission from mother to infant of “double-positive” mothers was 100% (10/10). No pregnancy complication was noted during the observation period, but in the control group the incidences of pregnancy complication were 16.67% (abortion), 43.02% (preterm), 15.62% (neonatal asphyxia), and 4.49% (fetal death), 10.0% (congenital anomaly). No HBV-positive newborn was detected and no developmental anomaly was found in the study group.

CONCLUSION: Lamivudine is helpful to prevent maternal-infant HBV transmission and may reduce the complications of HBV-infected pregnant patients.

INTRODUCTION
Through the world, over 300 million people have chronic hepatitis B virus (HBV) infection, and more than 75 percent of those affected are of Asian origin[1]. Chronic HBV infection causes cirrhosis, liver cancer, and death[2,3]. The disease is endemic in Africa and Asia, where the virus is transmitted from mother to newborn or between close contacts in early childhood[4,6].

Chronically infected persons with viral replication are at the highest risk for progressive liver disease[5]. In China, chronic HBV infection is a common clinical occurrence in pregnancy as well as a potentially serious condition[6]. In pregnant patients the complications of HBV occur more frequently and with a higher mortality[9]. Also vertical transmission of HBV to the infant is common[14,5]. Perinatal transmission of HBV is the most important cause of chronic HBV infection and remains one serious problem despite passive immunization (hepatitis B immune globulin at birth) and active immunization (hepatitis B vaccination according to the standard 3-dose schedule). In different studies high maternal HBV DNA levels were associated with a vaccination breakthrough[9,11]. Recently nucleoside analogues have been used to prevent mother-to-infant transmission of HIV-1[12]. In that setting, lamivudine given during the last weeks of pregnancy in HIV-1 and HBV positive women appeared to be safe[13,5]. Following a similar rationale, there was a clinical trial about the use of lamivudine, a potent inhibitor of HBV replication, in pregnant women with high HBV viral loads in highly endemic countries[16]. However, few data are available regarding the efficacy and safety of lamivudine treatment for chronic HBV from the early phase of pregnancy. Pharmaceutical inserts regarding lamivudine indicate it is of “uncertain safety” during pregnancy. In this retrospective analysis, we evaluated 38 cases of chronic HBV pregnant patients treated with lamivudine from the early phase of pregnancy for pregnancy-related complications and congenital anomalies.

MATERIALS AND METHODS

Patients
Forty-two chronic HBV-infected women were found to be pregnant during lamivudine treatment and presented to the physician between 2-3 mo of gestation. Then they were enrolled in the study. During the study, one patient chose to terminate her pregnancy, two stopped lamivudine therapy, and one was lost to follow-up. Thus the final study consisted of 38 pregnant patients who continued lamivudine therapy. The pretreatment diagnosis of HBV was based on National Prevention and Treatment Profiles of Viral Hepatitis (2000)[17] criteria with the following criteria: detectable HBsAg and HBeAg/HBeAb in serum, detectable serum HBV DNA, and elevated alanine aminotransferase (ALT) levels (more than 3-4 times normal level). Patients were excluded if they had hepatitis C or D infection. Patients had not received any other antiviral drugs in the preceding 6 mo. All patients were warned about that studies in rabbits had demonstrated lamivudine to result in fetal demise. However, it was also explained that the dosages used in animal studies were nearly 60 times higher than those used in humans (private communication).

Currently there is a clinical trial in Asia evaluating lamivudine use perinatally in mothers with high HBV viral
loads with the goal to reduce vertical HBV transmission to the infants[13]. The patients who earlier stopped lamivudine often experienced significant clinical deterioration. Thus overall we felt it appropriate to consider continuing lamivudine therapy. HBV infection in pregnant women was more serious than in non-pregnant women[9]. All the above were informed to any pregnant patients with HBV infection. Decision was made by patient herself on whether to terminate lamivudine treatment or not.

The data of complications of HBV hepatitis and HBV-positive babies were based on Prevention and Treatment of Viral Hepatitis study edited by Gao[19]. Lamivudine safety profile was obtained from international studies[13-15,18].

Regimen and parameters
Pregnant women with chronic HBV infection were treated with lamivudine. The dosage, course, efficacy evaluation, follow-up, measures to deal with resistant mutation were based on the Guideline for Lamivudine Clinical Use (2000)[20] and Expert Consensus on Lamivudine Clinical Use (2001)[21]. Complications of pregnancy included abortion, preterm birth, neonatal asphyxia, fetal death, and congenital anomaly[19]. Regular ultrasonic examination was carried out to monitor the safety of the fetus. All newborns were given the standard passive-active immunization or actively immunized at birth. Twelve babies were tested of HBV DNA (PCR), HBsAg, HBeAg, anti-HBs, anti-HBe, anti-HBc at birth before HBlg administration (T₀) and at the 6th mo (T₁) and the 12th mo (T₁₂) after birth. The health status and development of babies were assessed by the local children healthcare institution. All children were followed-up and documented.

RESULTS
Antiviral efficacy
HBV-DNA was converted to negative in 35 patients (92.11%) of the study group. HBeAg was converted to negative in 12 patients (31.58%). The rate of HBeAg seroconversion (loss of HBeAg or development of antibody to HBeAg) was 26.32% (10/38). The normalization rate of ALT was 73.68% (28/38). The rate of resistant mutation was 11.43% (4/35). Lamivudine was difficult to assess.

Incidence of HBV-positive baby (Table 1)
Twelve maternal-baby pairs were evaluated for HBV markers (HBsAg, HBeAg, anti-HBs, and anti-HBe anti-HBc) before and after delivery. All 12 mothers were double positive (HBsAg/HBeAg) before lamivudine treatment. Although the HBV-DNA parameters of all 12 mothers were converted to negative prepartum, 8 mothers remained HBeAg-positive, 1 HBeAg negative, and 3 reached seroconversion. The 8 mothers who were HBeAg-positive at childbirth, 3 babies were HBsAg-positive at birth (T₀), but turned negative at T₁ and T₁₂ postpartum. The other babies were all HBsAg-negative during 12 months of follow-up. Thus after one year, 100% of the babies were HBsAg-negative. But in control group, the blocking rates of active vaccine immunization for babies with double-positive (HBsAg/HBeAg) mothers were 74.07% with 30-30-10 µg doses of vaccine and 64.87% with 30-20-10 µg. The natural vertical HBV transmission from mother (double-positive) to infant was 100% (10/10)[19]. The prevention of HBV maternal-infant transmission was very significant in lamivudine-treated mothers.

Table 1 Blocking of maternal transmission in HBsAg and HBeAg double-positive mothers[16]

| n     | T₀ | T₁ | T₁₂ | HBsAg(+) | HBV-DNA(+) |
|-------|----|----|-----|----------|------------|
| Lamivudine treatment | 12 | 3  | 0   | 0        | 0         |
| Vaccine 30-30-10 µg | 81 | 21 | 21  | 21       | 74.07     |
| Vaccine 30-20-10 µg | 37 | 13 | 13  | 13       | 64.87     |
| Natural transmission | 10 | 10 | 0   | 10       | 0.00      |

Complications of pregnancy (Table 2)
The infants of lamivudine-treated mothers were delivered at full term without any complication. The incidence of pregnancy complication was lower in the study group than in the control group of pregnant mothers with chronic HBV[19].

Control of viral hepatitis activity (Table 3)
Although three out of 38 patients in the study group did not convert to HBV-DNA-negative within one year, ALT normalized in all three patients. Ten patients in the study group converted to HBV-DNA-negative, but their ALT remained abnormal. They were included in the pregnancy liver injury group. Six patients were HBeAg-negative, and four patients had seroconversion for HBeAb. A resistant HBV mutant emerged in four cases though their ALT remained normal. Thus overall hepatitis activity was controlled in all the study patients (100%). In the two patients who quitted lamivudine after the consultation, active hepatitis recurred within 6 months. Honkoop et al reported that the incidence of “lamivudine withdrawal hepatitis” was 17% (7/41)[22]. Hepatitis activity was better controlled in lamivudine treatment group than in the group who quitted lamivudine therapy (Table 3).

Infant development and health
Community maternal-child health clinics failed to detect any unfavorable outcome related to the infant’s health and development.

DISCUSSION
It has been well-known that the pregnant women chronically infected with HBV have more complications and a higher mortality during pregnancy[5,9]. Lamivudine has been found to be an effective treatment strategy for chronic HBV[15]. However, its use is not recommended during pregnancy especially during the first trimester because animal studies have demonstrated lethal effects on the rabbit fetus (private communication). In our study 38 pregnant women with chronic HBV infection continued lamivudine therapy during the entire pregnancy. Their decision to continue its therapy was voluntary.
after informed consent. They were all provided with information about the drug benefits and risks. Our results indicated lamivudine therapy not only provided a protective effect against maternal-infant HBV transmission, but decreased the likelihood of active HBV infection in the mother. Further complications were minimal compared with the control group. These results should be presented to a mother contemplating continuation of lamivudine therapy during pregnancy.

Pregnancy complications are likely caused by the activity of hepatitis B virus in mothers with chronic HBV infections. The rate of vertical maternal-infant HBV transmission was 90-100% in mothers who were double positive for both HBsAg and HBeAg. It is probable that such a high transmission rate has been led by the high viral load. The data in our study indicated lamivudine was able to neutralize hepatitis activity and reduction in the viral load might result in fewer pregnancy complications and prevent maternal-infant HBV transmission. This benefit may well outweigh the risk of lamivudine’s early toxic effects on the infant during the first trimester. Lamivudine has been found belonging to the L-form enantionmorph nucleotide analogue which is negatively selective for the human nucleotide. Toxicity was detected only at very high dosages of 1,000 times higher than the recommended human dosages. The dosage used in animals was 60 times greater than that used in human (private communication). Thus currently recommended lamivudine dosages for human may represent little risk to the pregnant mother.

However, there are several concerns about our current study. First, our study was not designed as a randomized-placebo-controlled study, thus any improvement in the study group could be due to such confounding factors as “self-selection” bias, or observer bias. Second, the study group was small and thus might lack power to distinguish a true difference between the treated group and the control group. However, we do consider the study to be of value in raising the question of benefit of lamivudine treatment of chronic HBV in pregnancy. Further studies, especially larger well-designed placebo-controlled studies are needed to confirm a true beneficial effect of lamivudine therapy for chronic HBV infection in pregnancy.

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