

HBV treatment and pregnancy

Jörg Petersen*

Liver Unit, IFI Institute for Interdisciplinary Medicine, Asklepios Klinik St. Georg Hamburg, Germany

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The management of hepatitis B virus (HBV) infection in pregnancy is complex. Because infection with HBV in infancy often leads to chronic disease, prevention of perinatal or vertical transmission is a major goal. Worldwide, vertical transmission remains the most frequent route of infection, particularly in endemic areas where up to 20% of women of childbearing age may have HBV. These women constitute a reservoir for perinatal transmission, which is associated with a very high rate of chronicity [1–3]. Without immunoprophylaxis, up to 90% of infants born to hepatitis B e antigen (HBeAg)-positive mothers become HBV chronically infected. However, the maternal screening programs and universal vaccination in newborns with active and passive immunoprophylaxis have dramatically reduced HBV transmission rates. But even with the use of appropriate prophylaxis with HBV immunoglobulin (HBIG) and HBV vaccination, a significant risk of vertical transmission remains, particularly in mothers with high viral loads and positive hepatitis B e antigen (HBeAg) status. In one series of mothers with high viral loads, this risk was as high as 28% [4]. An HBV DNA level greater than 10^7 copies/ml is an important risk factor for HBV transmission [5,6]. Wiseman *et al.* [7] recently studied 298 chronically HBV-infected women and their infants, who were vaccinated and who received HBIG. The infants were tested for HBV at 9 months of age and showed an HBV rate of 8.5% born to mothers with virus levels greater than $8 \log_{10}$ copies/ml. There is no indication to perform a caesarian section to reduce HBV transmission if vaccination and HBIG are administered accordingly.

Factors that influence treatment choices in women of childbearing age include safety in pregnancy and breastfeeding, efficacy of the agent, its barrier to resistance, length of therapy, and most important, the cause of treatment, i.e. treating the mother because of an advanced liver disease or treating the unborn child to prevent transmission.

If pregnancy is contemplated in near future, it may be prudent to delay therapy until after the child is born. This approach requires a careful assessment of the degree of hepatic activity and fibrosis. Although it is not to be used in the pregnant woman, interferon can be used in the woman of childbearing age, because therapy with this agent is for a defined period of 48 weeks and

often results in clinical remission [8]. This scenario is in contrast to the oral antiviral agents that generally require long-term therapy and result in lower rates of stable HBeAg seroconversion and some HBsAg loss only in HBeAg positive patients [9]. For those who require therapy, it is advisable to discuss the issue of pregnancy before starting the treatment.

No antiviral agent has been approved for use in pregnancy. Thus, when a woman on HBV antiviral therapy becomes pregnant, a decision needs to be made whether she should continue therapy for the duration of the pregnancy or if therapy should be withdrawn immediately. As with all decisions during pregnancy, the health of the mother and the fetus must be considered independently. From the perspective of the fetus, the major concern is the risk of exposure to medication during early embryogenesis. From the perspective of the mother, the major issue is whether stopping or switching medication will adversely affect both short- and long-term liver disease outcomes. In general, if the mother is known to have significant fibrosis, therapy should be continued because the risk of flare with withdrawal of therapy could result in reactivation and even decompensation of her liver disease. This effect on the mother's health could also impact the health of the fetus.

Decisions about initiating therapy during pregnancy again must include consideration of the risks and benefits for the mother and the fetus; furthermore, in which trimester the therapy should be started must be considered, too. Interferon has antiproliferative actions and is contraindicated during pregnancy. Furthermore, all polymerase inhibitors interfere with the replication of mitochondrial DNA, and this can result in mitochondrial toxicity leading to the lactic acidosis syndrome [10]. Although lactic acidosis syndrome is very uncommon in adults, less is known about the potential ramifications of mitochondrial toxicity in the developing fetus. These effects may be more diverse, because toxicity may affect organogenesis.

Of the nucleoside and nucleotide analogs indicated for the treatment of chronic HBV infection, all are classified as Food and Drug Administration (FDA) pregnancy risk category C except for tenofovir and telbivudine, which are category B. Most human experience with antiviral drug therapy in pregnancy has been with lamivudine. More than 4600 women have been exposed to the drug during their second or third trimester [11] and reported to the Antiretroviral Pregnancy Registry (APR). The APR monitors the safety of antiretroviral agents in the United States of pregnant women who have been exposed to lamivudine, tenofovir,

* Address: IFI Institute for Interdisciplinary Medicine, Asklepios Klinik St. Georg Hamburg, Lohmühlenstrasse 5, D-20099 Hamburg, Germany. Tel.: + 49 40 181885 3796; fax: + 49 40 181885 3788.

E-mail address: petersen@ifi-medizin.de.



Editorial

emtricitabine, or other antiviral drugs. Despite the large number of enrolled patients and reassuring results showing no significant increase in birth defects, there are limitations, including short follow-up and recording only defects identified at birth. Developmental anomalies (e.g. cardiac or neurologic defects) identified at a later date may therefore be omitted. Similar registries sponsored by the pharmaceutical industry have been severely limited by poor enrollment and provide little meaningful data. For the APR, no significant difference was reported in the rate of adverse outcomes if the initial exposure of any HBV drug was in the first trimester (2.7%) compared to the second or third trimester (2.5%) of pregnancy or compared to a non HIV nontreated general population.

Even though lamivudine is classified as FDA pregnancy risk category C, it is associated with the risk of birth defects that is not higher than the baseline birth defect rate. A meta-analysis of 10 randomized clinical trials (RCTs) examining 951 HBV carrier mothers was reported to evaluate the efficacy of lamivudine in reducing in utero transmission of HBV [12]. The RCTs evaluated included newborns who received immunoprophylaxis at birth and women who were treated with lamivudine from 24 to 32 weeks of gestation, until delivery to 1 month post-delivery. Newborns in the lamivudine group had a 13–24% significantly lower incidence of intrauterine exposure and a lower perinatal infection rate at 9–12 months. This report was limited by the quality of the studies included. On the other hand, in a recent poster presented at EASL 2011 in Berlin [13], Ayres *et al.* showed that although the therapy with lamivudine achieved an HBV DNA load reduction of $3 \log_{10}$ IU/ml, in 20% of the pregnant women, the viral load remained high ($>1 \times 10^7$ IU/ml) and resistant mutations were detectable only after three months of therapy, calling for more potent antiviral drugs to be used to prevent transmission.

Of the two agents classified as FDA pregnancy risk category B, only tenofovir received this classification based on the data collected in human exposure, so far. There have been no other published studies using entecavir, adefovir, or emtricitabine for preventing HBV vertical transmission, and these drugs should be switched immediately, if a woman becomes pregnant.

The experience with tenofovir in pregnant women consists of 606 women in their first trimester and 336 in their second trimester from the APR. The rate of birth defects associated with tenofovir ranges from 1.5% (second-trimester use) to 2.3% (first-trimester use), which is again similar to the background rate. Telbivudine received its pregnancy risk category B rating based on animal studies; there were few human pregnancy registry data up to now.

In this issue of the *Journal of Hepatology*, Han *et al.* present a prospective study [14] that evaluates the efficacy of telbivudine for preventing HBV newborn infection performed in 230 pregnant HBsAg positive patients with HBV DNA levels of $>1.0 \times 10^6$ copies/ml. The study shows that telbivudine plus vaccination is superior to HBIG and HBV vaccines only in newborns to prevent HBV transmission (0% vs. 8%). This study reconfirms data from a recent study of 31 pregnant women in China, treated with telbivudine started at weeks 28–32 of pregnancy and continued to 30 days postpartum [15]. All babies received active and passive immunoprophylaxis. The infection rate was 0% in those treated with telbivudine and 13.3% in the untreated controls.

The advantages of the study by Han *et al.* are the use of telbivudine, a more potent antiviral drug than lamivudine with a lower risk of HBV drug resistance and the inclusion of a large

number of pregnant HBsAg positive women. The disadvantages are the short follow up, only seven months after delivery, and the lack of results of virologic breakthrough and resistance data. Furthermore, it is not a randomized study, patients were allocated depending on their own wishes and prophylaxis was started either during the second trimester or during the third trimester but without a definitive time point. It is unclear whether mothers with high levels of viremia started earlier compared to those with low levels of viremia. The risk of HBV transmission could have been analyzed even better in relation to the time of starting prophylaxis in addition to HBV DNA levels. The primary end point of the study was defined as undetectable HBsAg and HBV DNA at birth and at month 7. This is a short period of follow-up to analyze HBV perinatal transmission, at least newborns should be followed for 1 year. Nevertheless, this study is adding very important information to our very limited knowledge of safety of polymerase inhibitors in pregnant women and helps to support the “B” rating of telbivudine.

Rather than switching agents, withdrawal of treatment for the duration of pregnancy may be preferable in some cases, especially to the mother who wants to avoid any potential future risk to the fetus. What would be the consequence to the mother of stopping treatment completely? The natural history of chronic HBV in pregnancy has not been well described. Limited data exist to suggest that, rarely, severe complications of HBV occur late in pregnancy, with reports of liver failure in previously asymptomatic individuals [16]. Data specifically addressing the risk of stopping therapy during pregnancy are only anecdotal.

Overall, it appears that the risk of an adverse outcome with continuing antiviral therapy during pregnancy is likely to be very low. However, therapy could be discontinued with close observation of the mother to avoid continued fetal exposure during the first trimester, especially in the patient who does not have advanced fibrosis.

When deciding on starting therapy in the third trimester, the perinatal transmission outcome of prior pregnancies should be considered. If previous pregnancies did not result in perinatal transmission, then a viral load of greater than 10^7 copies/ml should be used to determine if therapy should be initiated (similar to women who had no children). However, if perinatal transmission did occur with a prior pregnancy, then the risk of perinatal transmission in the current pregnancy is likely higher. In such cases, strong consideration for initiating therapy in the third trimester is recommended, regardless of the mother's viral load at the end of the second trimester.

Despite the position from the American Academy of Pediatrics stating that breastfeeding is not contraindicated in naïve women with HBV if HBIG and vaccination have been administered accordingly [17], for mothers on antiviral therapy, breastfeeding cannot be recommended. According to prescribing information, it has not been recommended that women breastfeed their infants while taking lamivudine or tenofovir, to avoid risking postnatal transmission of HIV-1 infection (package inserts lamivudine and tenofovir). Although it is known that lamivudine and tenofovir are both excreted into human breast milk, little is known about the extent of exposure of antiviral agents during breastfeeding. Thus, little is known about the overall safety of breastfeeding in this setting.

In summary, treatment of HBV infection during pregnancy remains a challenge, the risks and benefits must be weighed carefully and there are still numerous gaps in our knowledge. The

benefits of treatment appear to be most pronounced in cases with high maternal viremia to prevent transmission and in mothers with advanced fibrosis to prevent flares. Viable treatment choices are limited to lamivudine, tenofovir, and telbivudine. Of these, lamivudine and tenofovir appear to be the therapeutic options with reasonable human exposure and safety data in pregnancy and we do see now an increasing number of data for the safety of telbivudine, too.

Conflict of interest

The author declared that he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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