EDITORIAL

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Further standardization and safety issues for antiviral therapy during pregnancy

Use of hepatitis B vaccine universally for all newborn infants in China and the vaccine plus hepatitis B immunoglobulin (HBIG) for infants born to hepatitis B surface antigen (HBsAg) positive mothers is a nationwide procedure for prevention of mother-to-child-transmission (MTCT) of hepatitis B virus (HBV), and this strategy has significantly reduced the rate of MTCT. However, does that mean that the MTCT is reduced to very low level? Not yet. The rate of MTCT was as high as 7.1% among HBsAg and hepatitis B e antigen (HBeAg) positive mothers, according to the review article published by Professor Yu and her coauthor Dr. Hu in this issue of the journal, and there are still problems to solve to further reduce the MTCT in China.[1]

Dr. Yu and Hu's article provides much important information pertaining to the epidemiology, findings and achievements of the studies for decreasing the rate of MTCT, the mechanisms of MTCT of the HBV, and future studies and developments in this field. To prevent the immunoprophylaxis failure, and to achieve possible lowest MTCT rate, pediatricians/obstetricians responsible for hepatitis B in pregnant women and infants and children need to apply the best or optimized antiviral therapy for the pregnant women who are positive for both HBsAg and HBeAg. On the other hand, there has been a great concern on the safety issues of the fetuses/infants regarding the nucleoside analogues. We need to further understand the safety of antiviral therapies against HBV in the infants born to HBV carrier mothers.

Before we apply the antiviral therapy for a pregnant woman, we should clarify the following issues. 1) Do we need to give antiviral treatment to all the pregnant women who are positive for HBV DNA? Or we need to have a threshold value, and using it to choose the target patients? Cheung et al's[2] recently published review article provides answer to this question: the guidelines of three major academic organizations in the world, i.e., American Association for the Study of Liver Diseases (AASLD), European Association for the Study of Liver (EASL), Asian Pacific Association for the Study of the Liver (APASL) provide important reference for the threshold, the gestational age to start the therapy, etc. The threshold of the American and European associations are 200 000 or 2×10^5 IU/mL, but the APASL (Asian-Pacific) guideline recommends 6–7 $\log_{10}$ IU/mL, which is $1 \times 10^6 - 1 \times 10^7$ IU/mL, much higher than the American and European threshold. 2) The gestational age to start the antiviral therapy is another important factor to consider; the three major associations have similar recommendation, 28 (or 24) weeks to 28 to 32 weeks. 3) Which antiviral agent is the best? Tenofovir is the drug of choice, while telbivudine can be an alternative. 4) The mode of delivery may have certain effect on the rate of MTCT of HBV. Yang et al[3] reported in a meta-analysis of 28 articles that cesarean delivery was associated with lower MTCT rate (6.76%) than that of vaginal delivery (9.31%, $P < 0.001$). Cesarean delivery is not considered by the American guideline, and the European and Asian guidelines did not mention about the mode of delivery. 5) An important question is that when the antiviral therapy should stop. There is no consistent decision, the therapy either can stop shortly or up to 12 weeks after delivery. 6) The final question is breast feeding; according to the US and European guidelines, breast feeding is not contraindicated; however, the Asian guideline does not encourage breast feeding during antiviral treatment. In practice, the doctor may explain pros and cons of breast feeding and make a final decision with the parents.

Safety of the fetus/infant is a major concern with regard to antiviral therapy. Study demonstrated that use of lamivudine or telbivudine was not associated with increased risk of congenital malformation and other maternal or neonatal complications such as post-partum hemorrhage, cesarean delivery, elevated creatine kinase, preterm birth and low Apgar scores. It seemed that in Asian countries telbivudine has been used more frequently than tenofovir.

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In a prospective cohort study, which paid closer attention to the safety of the antiviral treatments, the rates of neonatal congenital abnormalities among infants born to mothers who had serum HBV DNA > 10^6 IU/mL during pregnancy and treated with tenofovir, telbivudine or without antiviral treatment were 2.4%, 0.6% and 2.3%, respectively, and the differences were not statistically significant (P = 0.140).[4] The study had limitations of small sample size, lack of information of early pregnancy, etc.

Since tenofovir is the most frequently applied antiviral agent for the purpose of reducing MTCT transmission of HBV, the safety issue of this agent became the focus of concern. Creatine kinase was found elevated in the pregnant women although most were asymptomatic. Side effects of tenofovir was mild and mostly subsided; it did not affect rates of cesarean delivery, postpartum hemorrhage and preterm delivery. Risk of birth defect was similar to the background risk, no teratogenic effect or congenital anomaly was noted by a systematic review. However, long-term observations and studies are needed for further understanding of the safety issues related to the perinatal and early pregnancy use of tenofovir.

In summary, in addition to postnatal use of hepatitis B vaccine and HBIG, antiviral therapy with tenofovir or telbivudine become universally accepted practice for reducing MTCT of HBV although the treatments need further standardization and continuous and close attention should be paid to maternal as well as fetal/infants safety.[5,6]

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CONFLICT OF INTEREST

None.

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