Evidence against in utero transmission of hepatitis B virus

Yi-Hua Zhou

I read with interest a recent Review by Terrault et al. on viral hepatitis and pregnancy (Terrault, N. A. et al. Viral hepatitis and pregnancy. *Nat. Rev. Gastroenterol. Hepatol.* **18**, 117–130 (2021))[1]. Although the authors clearly stated that mother-to-child transmission (MTCT) of hepatitis B virus (HBV) primarily occurs during the peripartum period, they also stated that in utero transmission could account for the 10% failure rate of neonatal vaccination[1]. However, the accumulating evidence to date seems to argue against the existence of HBV in utero transmission.

First, administration of hepatitis B immunoglobulin (HBIG) and HBV vaccine can completely block MTCT in infants of HBV-carrier mothers who are HBV e antigen (HBeAg)-negative[2–4], which indicates that there is no HBV in utero transmission in pregnant women who are HBeAg-negative carriers because HBV in utero transmission cannot be prevented at all by immunoprophylaxis in infants.

Second, administration of oral anti-HBV agents started at 28–32 weeks of gestation in pregnant women with positive HBeAg status and/or high HBV DNA levels, in combination with neonatal immunoprophylaxis, almost completely prevents MTCT of HBV[5,6]. These results indicate that maternal HBV, even at high levels, cannot transplacentally enter into the fetus before 28 weeks of gestation, because the antivirals cannot cure in utero transmission that has 'already occurred'. This observation is in agreement with the findings that acute maternal HBV infection in the first or second trimester of pregnancy rarely caused HBV infection in infants[7], although viraemia in acute HBV infection is usually high. In addition, pregnant women with HBV infection who have received antivirals during late pregnancy still have viraemia[5,6]. Thus, the observations that almost no HBV infection occurs in infants born to the treated pregnant women suggest no occurrence of in utero transmission.

Third, after administration of the immunoprophylaxis within one hour after birth in infants of mothers who are HBeAg-positive and who did not receive antivirals during pregnancy, MTCT of HBV was reduced to 1.2–2.4%[4–6], which is much lower than the reported rate of 4.5–12% in infants who received the recommended immunoprophylaxis within 12 or 24 hours after birth[2,3], providing evidence that a great proportion of immunoprophylaxis failure is not caused by in utero transmission.

Fourth, the total absence of anti-HBc IgM in newborns of mothers with HBV infection argues against the presence of in utero transmission[8,9].

Lastly, a prerequisite of in utero transmission is placental barrier damage caused by the microbial pathogen. However, HBV is not cytopathogenic and to date there is no report to show that HBV can damage placenta. Theoretically, the placental barrier might block the entry of HBV into fetus.

Therefore, HBV in utero transmission seems to not occur. Clarification of this issue would help clinicians take more reasonable interventions to prevent MTCT of HBV. Although studies demonstrate that administration of antivirals started at week 28–32 of gestation almost completely prevent MTCT of HBV, earlier use started at week 24–28 of gestation is still being proposed[10], probably because of concerns about in utero transmission.

There is a reply to this letter by Terrault, N. A., Cheung, K. W., Levy, M. T. & Jourdain, G. *Nat. Rev. Gastroenterol. Hepatol.* https://doi.org/10.1038/s41575-021-00456-y (2021)

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Competing interests
The author declares no competing interests.

Reply to 'Evidence against in utero transmission of hepatitis B virus'

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We would like to thank Zhou for their correspondence on our Review (Terrault, N. A. et al. Viral hepatitis and pregnancy. *Nat. Rev. Gastroenterol. Hepatol.* **18**, 117–130 (2021))[1] and for an opportunity to expand on in utero transmission of hepatitis B virus (HBV) (Zhou, Y.-H. Evidence against in utero transmission of hepatitis B virus. *Nat. Rev. Gastroenterol. Hepatol.* https://doi.org/10.1038/s41575-021-00455-z (2021))[2]. Although the estimate of 10% incidence might be high, we believe there is ample evidence to support in utero HBV infection.

In utero infection via germline is possible. HBV DNA could be detected in ova of women with HBV infection[3] and in embryos of hepatitis B surface antigen (HBsAg)-discordant couples[4]. Placental infection is another mechanism of in utero infection, with HBV (detected by in situ hybridization) found in a gradient of infected placental cell layers from the maternal to the fetal side and presence of placental HBV DNA, particularly in endothelial cells, associated with fetal infection in newborns[5]. Fetal contamination by maternal blood during invasive prenatal