Evidence against in utero transmission of hepatitis B virus

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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 vaccination¹. 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 infants⁷, 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 proposed¹⁰, 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)

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 infection³ and in embryos of hepatitis B surface antigen (HBsAg)-discordant couples⁴. 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 newborns⁵. Fetal contamination by maternal blood during invasive prenatal

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Competing interests

The author declares no competing interests.

tests could also be a cause of in utero infection, with maternal HBV DNA levels greater than 6-log IU/mL or presence of hepatitis B e antigen (HBeAg) defining a higher risk of in utero infection⁶.

Clinical studies also support the plausibility of intrauterine infection. In a large, randomized trial of tenofovir disoproxil fumarate (TDF) versus placebo, two of three infants who acquired HBV infection, all in the placebo arm, had a very high HBV DNA load on the day of birth. This observation is difficult to explain unless there was established infection prior to birth⁷. Similarly, another study found that infant birth blood HBV DNA positivity was significantly lower in TDF-treated mothers than in untreated mothers (6% versus 31%)⁸. These studies highlight the role of maternal antiviral therapy in reducing intrauterine infection.

It is important to emphasize that exposure to HBV in pregnancy does not equate with infection. HBsAg, HBeAg, anti-HBe, anti-HBc and HBV DNA are detectable in amniotic fluid from 16–23 weeks and in fetal blood from 24–32 weeks of gestation, but only a minority have post-natal infection⁹. Embryonically, liver development with production of bile is evident only after 12 weeks gestation; when fetal hepatocytes can support HBV replication is unknown. Studies have shown that fetal HBV exposure through the placenta can induce innate immune cell maturation with a predominant T helper 1 cell profile and suppression of proinflammatory cells¹⁰. Prolonged fetal exposure to maternal HBeAg

through the placenta coupled with the high cross-reactivity of HBeAg and HBcAg, in terms of T helper cell recognition, might account for the lack of anti-HBc immunoglobulin M in newborns. Further, the altered immune milieu in utero (compared with adult-acquired infection) might account for the absence of symptomatic acute HBV infection in newborns.

Provision of third trimester maternal TDF therapy and timely neonatal immunization have reduced mother-to-child transmission (MTCT) to very low rates (<1%)¹. The rare cases of prophylaxis failure might be the consequence of in utero infections when fetal hepatocytes are susceptible to HBV and/or with compromise of the placental barrier. Given the safety of TDF in pregnancy, we believe consideration of earlier antiviral treatment during pregnancy in certain high-risk women is warranted.

Thus, while the predominant risk of MTCT of HBV occurs peripartum, there is strong evidence for the existence of in utero infection and the continued efforts to improve prophylactic measures, including consideration of maternal antiviral therapy earlier than the third trimester, might reduce MTCT to zero.

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Competing interests

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