CASE REPORT

Indications for antiviral therapy for chronic hepatitis B in pregnant mothers

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SUMMARY

The use of antiviral therapy for chronic hepatitis B virus (HBV) infection in the setting of pregnancy needs to be individualised based on limited data. We report a case of a 34-year-old Korean-American woman with a history of pregnancy with emergent caesarean section due to prolonged labour in the setting of HBV e-antigen (HBeAg) positive chronic HBV with a pretreatment baseline HBV DNA level of 110000 000 million copies per mL. Her first delivery was complicated by mother-to-child transmission (MTCT) of HBV infection to her daughter despite standard active and passive immunoprophylaxis. Our case report highlights an important clinical decision-making step regarding the timing of antiviral therapy in the management of chronic HBV in pregnant women with high risk of MTCT.

pretreatment baseline HBV DNA level of 110 million copies per mL.

First pregnancy

Our patient delivered her first baby, a daughter, at age 28. During her first pregnancy, she was recommended to schedule standard active and passive immunoprophylaxis with hepatitis B immune globulin and hepatitis B vaccination for her baby, to be administered within 12 hours of birth, followed by additional two doses to complete the vaccination series. Her baseline HBV DNA level was 110 million copies per mL with HBeAg positivity. Owing to prolonged labour, she underwent an emergent caesarean section. She delivered a baby girl, who was later noted to have the presence of hepatitis B surface antigen (HBsAg) and high levels of HBV DNA.

Second pregnancy

Two years later, at age 30, she became interested in pursuing a second pregnancy. Our patient decided to start antiviral therapy 6 months prior to conception and remained on antiviral therapy during the entire course of her second pregnancy to minimise the risk of MTCT. Prior to her second pregnancy, our patient did not have signs of active chronic hepatitis, as was the case in her first pregnancy. However, she was noted to have intermittent elevations in her aminotransferase levels. She pursued therapy because her first pregnancy led to a vertical transmission of HBV. She was placed on antiviral therapy—tenofovir disoproxil fumarate (TDF) 300 mg a day—6 months prior to her second pregnancy and demonstrated a rapid decline in HBV DNA to <100 copies/mL, but persistently positive HBsAg and HBeAg. Subsequently, she became pregnant and delivered a healthy baby boy through elective caesarean section. Active and passive immunoprophylaxis were instituted. Her second child, the healthy son, was noted to have no evidence of active HBV infection. Vaccination series was completed, and he demonstrated evidence of successful immunisation. HBsAg was undetectable in her son's serum, and her son's cord blood was not tested for HBsAg. Her son did not demonstrate any evidence of chronic HBV infection 4 years after his birth. HBsAg was measured qualitatively and not quantitatively due to unavailability of quantitative HBsAg assay at our facility.

Our patient was noted to have evidence of stage II fibrosis on ultrasound elastography. Therefore, she decided to continue antiviral therapy to prevent progression of histologic damage within

BACKGROUND

The risk of developing chronic hepatitis B virus (HBV) infection is strongly related to the age of exposure, with 90% risk of vertical transmission in infants, up to 50% risk of infection in toddlers and young children, and 5% risk of infection in adults in the absence of immunity.¹ Standard active and passive immunoprophylaxis prevents transmission in 95% of cases. Mother-to-child transmission (MTCT) rates can vary significantly based on the presence or absence of certain predictors. Potential risk factors related to the failure of immunoprophylaxis include high-level HBV viremia, HBV e-antigen (HBeAg) positivity, intrauterine infection, previous history of vertical transmission despite active-passive immunoprophylaxis, emergent caesarean section and mutations of HBV surface protein.²

Maternal HBeAg status is associated with MTCT—with a 70–90% transmission rate in HBeAg positive mothers and 10–40% transmission rate in mothers who are negative for HBeAg.² While HBeAg status is associated with MTCT, it is an indirect marker for HBV replication and there are HBV variants with negative HBeAg, which can cause fulminant hepatitis. The threshold for antiviral therapy is dependent on HBV DNA levels (>1 000 000 copies/mL or >200 000 IU/mL).³ Recent data have demonstrated that active-passive immunoprophylaxis fails to prevent the transmission of HBV infection in 8–30% of children born to mothers with high-level HBV viremia.⁴

CASE PRESENTATION

We present a 34-year-old Korean-American woman with HBeAg-positive chronic hepatitis B with

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her liver and to optimise the suppression of HBV replication. Her preference was to continue antiviral therapy indefinitely to avoid HBV flare-up noted in small proportion of these patients with abrupt discontinuation of therapy. She did not breastfeed her son and continued antiviral therapy without interruption. She remains chronically infected with HBV DNA levels persistently <100 IU/mL, positive HBsAg, positive HBeAg, positive total (IgG and IgM) anti-HBc, negative anti-HBs and negative anti-HBe. Her liver enzymes remain normal since the inception of antiviral therapy.

INVESTIGATIONS

Her laboratory data showed normal white cell count, haemoglobin, haematocrit, platelet count, electrolytes, blood urea nitrogen, creatinine, glucose, total bilirubin, aminotransferases, alkaline phosphatase and albumin. She was found to have HBV genotype C. HBV DNA was persistently detectable at <100 IU/mL, and HBsAg was positive. Ultrasound of the abdomen did not reveal any focal hepatic lesions suspicious for hepatocellular carcinoma.

OUTCOME AND FOLLOW-UP

Our Korean-American mother remains clinically stable from a liver standpoint and does not show evidence of hepatic decompensation. She has been noted to have stage 2 fibrosis on hepatic elastography. Therefore, she will continue antiviral therapy long-term. She will continue to undergo hepatoma surveillance every 6 months with ultrasound of the abdomen and an α -fetoprotein check. Her daughter (first child) remains clinically stable in the immune tolerant phase with high levels of HBV DNA and positive HBeAg. Her daughter is also undergoing hepatoma surveillance every 6 months. Antiviral therapy for her daughter will be considered later in life if indicated. Repeated tests on her son (second child) showed no evidence of HBV infection and serological markers confirmed immunity.

DISCUSSION

The current standard of active and passive immunoprophylaxis is thought to be 95% effective in preventing transmission of HBV from mother to her child; however, data suggest this may be an overestimation, especially in certain clinical scenarios. This ambiguity is especially difficult for patients who are already aware of their hepatitis B status and who wish not to pass down HBV infection to their newborn children. [Box 1](#) highlights the potential causes for the failure of immunoprophylaxis.²

Emergent caesarean section, high levels of hepatitis B DNA and HBeAg positivity

HBeAg is a marker of HBV replication and infectivity; the presence of HBeAg is usually associated with high levels of HBV DNA in serum and higher rates MTCT. Our patient with high HBV DNA levels transmitted the virus to her first-born child after undergoing an emergent caesarean section despite appropriate immunoprophylaxis. A study looking at ~1400 infants born to HBsAg-positive mothers who received appropriate immunoprophylaxis at birth reported MTCT rates of 1.4% in elective caesarean delivery, 3.4% in vaginal delivery and 4.2% in urgent caesarean delivery ($p<0.05$).⁵ In a similar light, a large clinical trial conducted in Zambia looked into tenofovir for the

Box 1 Potential causes for failure of immunoprophylaxis

- ▶ Hepatitis B virus (HBV) DNA higher than 1 000 000 copies (200 000 IU)/mL
- ▶ HBeAg positivity
- ▶ Previous history of failed active-passive immunoprophylaxis
- ▶ Emergent caesarean section
- ▶ Intrauterine infection
- ▶ Mutations of HBV surface protein

HBV = hepatitis B virus; MTCT = mother-to-child transmission.

Figure 1 Management algorithm for chronic hepatitis B and pregnancy.

prevention of HIV MTCT.⁶ When stratified according to HBV DNA levels, those with low levels (<1 million copies/mL), the delivery modality did not impact MTCT. Although not conclusive, this may suggest that delivery modality affects MTCT in patients with high levels of hepatitis B viremia (>1 million copies/mL).

Management algorithm for chronic hepatitis B and pregnancy

The important decision to start or hold antiviral therapy for chronic HBV infection during the last 8 weeks of pregnancy may be approached systematically (figure 1) with relevant laboratory values and understanding of the potential causes of failure for immunoprophylaxis.

Previous history of vertical transmission despite active-passive immunoprophylaxis

In our patient's first pregnancy, MTCT was not preventable despite the institution of comprehensive active and passive immunoprophylaxis for the birth of her daughter (first child). While previous history of vertical transmission despite immunoprophylaxis may be a risk factor for failure of immunoprophylaxis, the mother was able to deliver a healthy boy without MTCT with a change in the modality of delivery (emergent caesarean section to elective section) and antiviral therapy—

TDF 300 mg/day. This finding is consistent with recent report by Pan *et al*³ looking into the effectiveness of TDF 300 mg/day for mothers with positive HBeAg and HBV DNA > 200 000 IU/mL in preventing MTCT of HBV. Pan *et al*³'s study also found that only 66 of 97 women reached HBV DNA level <1 000 000 copies/mL, likely due to the short duration of treatment which started at week 32; this suggests that TDF regimen 8 weeks prior to delivery or ideally prior to pregnancy, as with our patient, is the best approach. After treatment prior to her second pregnancy, our patient's HBV DNA levels were consistently below 100 IU/mL. Although Pan *et al* did not directly analyse the effects of the modality of delivery in prevention of MTCT, this study in conjunction with our case report raises the question whether the modality of delivery (emergency caesarean section vs non-emergent) and reduction of viral replication in pregnant women with HBV DNA levels >200 000 IU/mL are the important factors to consider when trying to prevent MTCT of HBV in a pregnant woman.

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Competing interests None declared.

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Learning points

- ▶ Active-passive immunoprophylaxis fails to prevent the transmission of HBV infection in 8–30% of children born to mothers with levels of HBV DNA higher than 1 000 000 copies (200 000 IU)/mL.
- ▶ Maternal HBeAg positivity is associated with higher rate of mother-to-child transmission (MTCT).
- ▶ Delivery modality (vaginal delivery, elective caesarean section and emergent caesarean section) may affect MTCT in patients with high levels of HBV DNA levels.
- ▶ Antiviral therapy against chronic hepatitis B can reduce the risk of MTCT in high-risk mothers.

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