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Letters to Editor

High Level of HBV DNA Virus in the Breast Milk Seems not to Contraindicate Breastfeeding

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Dear Editor,

Breastfeeding is recommended by the World Health Organization regardless of mother's hepatitis B virus (HBV) status since breast milk is not considered as an efficient pathway for HBV perinatal transmission.¹ However, concerns about a possible risk of HBV transmission through breastfeeding arises under conditions favoring an increase of HBV DNA viral load in breast milk, particularly among unvaccinated children.^{2,3}

We present here a case of an HIV-HBV co-infected mother who exposed her child to a significant HBV infectious inoculum via breast milk, likely due to a hepatitis flare or an acute HBV infection.

The mother-child couple was enrolled in the Kesho Bora study; a randomized controlled trial evaluating maternal prophylactic strategies to reduce HIV transmission through breastfeeding.⁴ At week 6 post-delivery, a > ten fold elevation of alanine transaminase (ALT: 750 IU/L) was observed in a 20 years old mother. This mother was included in the control arm receiving short course antenatal zidovudine and single-dose intrapartum nevirapine in accordance with per national guidelines at the time. Serological testing confirmed HBV infection (positivity for HBsAg) and ruled out hepatitis A and C infections. Serum and

breast milk samples were retrospectively assessed for for HBV DNA levels at week 2 at week 2 and 12 using a standardized qPCR method (HBV Generic PCR, Omunis, Montpellier, France). Significant levels of HBV DNA were found in both left and right breast milk samples at week 2 post-delivery ($> 10^3 \log_{10}$ HBV DNA IU/mL) whereas, ALT level was normal (12 IU/ml). HBsAg levels were also quantified in breast milk ($>10^1$ IU/ml) using a quantitative assay (Architect HBsAg QT assay, Abbott, Chicago, IL). A dramatic decrease in the levels of HBV DNA and HBsAg was observed in both serum and breast milk at week 12 post-delivery (**Table 1**). Serum and breast milk became negative for HBsAg 6 months after delivery without detection of anti-HBs antibody. The newborn was infected neither by HIV nor by HBV despite a vaccine schedule starting at week 6. Protective anti-HBs titers were observed in response to HBV vaccination (>10 mIU/mL) at month 12. We estimate that the intestinal mucosa of the infant was in contact with more than one million HBV particles/per day based on a daily consumption of 300 ml during the first weeks of life. Although HBV infection is a major health concern worldwide, very few studies have explored HBV DNA in breast milk.

Table 1.

| | W2 post delivery | | | W12 post delivery | | |
|------------------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|
| | Plasma | BM right | BM left | Plasma | BM right | BM left |
| HBV DNA PCR (IU/mL) | 7.36 x 10 ⁹ | 6.60 x 10 ³ | 4.27 x 10 ³ | 3.69 x 10 ² | <1 x 10 ² | <1 x 10 ² |
| HBsAg detection | Positive | Positive | Positive | Positive | Negative | Negative |
| HBsAg level (IU/mL) | 1.25 x 10 ⁵ | 1.10 x 10 ¹ | 1.51 x 10 ¹ | 2.32 x 10 ¹ | <0.05 | <0.05 |
| HBeAg detection | Positive | Positive | Positive | Positive | Negative | Negative |
| HIV RNA (copies/mL) | 1.82 x 10 ⁴ | 2.81 x 10 ² | 4.71 x 10 ³ | 2.25 x 10 ⁴ | 1.24 x 10 ³ | 6.67 x 10 ² |
| ALT (IU/L) | 26 | | | 17 | | |
| CD4 T cells count (cells/ μ L) | 426 | | | 311 | | |

BM: acellular breast milk

<1 x 10² HBV DNA IU/mL: detected but not quantified

HBV DNA has been detected in the colostrum of mothers tested positive for HBe antigen using PCR and Southern blot hybridization⁵ and in banked human milk samples using a nested PCR⁶.

Recently, HBV DNA was tested in serum and breast milk using a standardized quantitative PCR method in HIV-HBV coinfecting mothers who were under lamivudine-containing antiretroviral regimen from the 25th week of pregnancy⁷. At delivery, 11/26 (42%) women had significant HBV DNA levels in serum (ranging from 3.3 to >8 log₁₀ IU/mL) that steadily decreased at months 1, 3, and 6 postpartum (median of 5.2, 4.5 and 2.8 log₁₀ IU/mL respectively). HBV DNA was detected in breast milk from three HBV viremic women (33%) and four out of 24 breast milk samples (17%). When detectable, HBV DNA levels in breast milk were low in all cases ranging from 1.18 to 2.20 log₁₀ IU/ml, suggesting that level of HBV DNA in breast milk might always be negligible. The rate of HBV infection was also assessed among 23 HIV-HBV exposed children along the two years study period. Diagnosis of transient HBV infection was made in four children whereas other three children acquired HBV infection during the postnatal period (first HBsAg positive test at 12 months in one case and 24 months in the other two cases). Pirillo et al observed that those 7 children were exposed to the highest HBV infectious inoculum, not only at delivery, but also during all the postnatal period, since their mothers presented the highest levels of HBV DNA in serum. However, no correlation was found between HBsAg positivity and HBV DNA levels in breast milk.

In our case, exposure to a larger amount of HBV infectious particles via breast milk was detected, but the child, who was correctly vaccinated, was not infected with HBV. This result seems to confirm that breastfeeding is not an effective route of HBV transmission during the perinatal period, as previously reported in clinical studies.^{2,3} However, in contrast with the results of Pirillo et al, our data show that HBV exposition via breast milk could be significant,

especially during a high HBV replicative phase. HBV exacerbations or hepatitis flares often occur among chronic HBV infected mothers after pregnancy leading to higher levels of HBV replication in the blood^{8,9}. In our case, an accurate differential diagnosis between an acute HBV infection and a hepatitis flare could not be made since the time of HBV infection was unknown. A typical elevation of ALT 6 to 10 weeks after delivery preceding the upsurge of HBV DNA levels suggested a hepatitis flare.¹⁰ However, this mother also experienced HBsAg clearance within six months, as often occurs in acute HBV infections.¹¹

Hepatitis flares or acute HBV infections in chronic HBV infected patients do not usually require antiviral treatment since most of the episodes resolve spontaneously.¹² In pregnant women, the risk of fulminant or severe hepatitis following hepatitis flares or acute HBV infections does not appear increased (9). However, as in general population, those episodes may progress to a fulminant liver failure and must be treated with nucleot(s)ide analogs and be evaluated for liver transplantation.^{12,13} Due to its safety and better resistance profile, Tenofovir is currently the antiviral of choice for the treatment of severe acute HBV infection, and its efficacy has been demonstrated even in cases in which previous nucleoside analog treatment as lamivudine had failed.¹⁴ Hence, Tenofovir provides a better efficiency during a hepatitis flare or a post-delivery acute HBV infection.

Exposure to a significant HBV infectious inoculum through breastfeeding should not always be considered negligible in children from HIV-HBV coinfecting mothers who do not receive any active antiviral treatment against HBV. However, cumulative exposure during lactation does not seem to contraindicate breastfeeding among correctly vaccinated children despite the immaturity of their intestinal mucosa.

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