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REVIEW

Breastfeeding and chronic HBV infection: Clinical and social implications

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Abstract

Mother-to-child transmission of hepatitis B virus (HBV) is among the most important causes of chronic HBV infection and is the commonest mode of transmission worldwide. Currently, the presence of HBsAg, HBeAg and HBV DNA in breast milk is confirmed. Several studies have reported that breastfeeding carries no additional risk that might lead to vertical transmission. Beyond some limitations, the surveys have not demonstrated any differences in HBV transmission rate regarding feeding practices in early childhood. Promotion of breastfeeding is substantial, especially for low-income individuals and regions with uncertain, unfeasible, and unsafe water supplies. Lactoferrin, minimal inflammation or activation within the infant gut during exclusive breastfeeding, and nonspecific biological molecules in the milk are identified as major factors of breast-milk defense. This review discusses preemptive antiviral therapy during pregnancy and lactation. Long-term follow up of breast-milk HBV concentrations and correlation with serum viral load; nucleos(t)ide analogue concentrations in breast milk in HBV-positive mothers in the setting of chronic HBV infection; safety of antiviral therapy during pregnancy and lactation; and the difference in viral load in the milk in exclusive or non-exclusive breastfeeding are still open questions. The paper reviews the current data and outlines the course of further investigation into this often underestimated issue.

Key words: Breastfeeding; Lamivudine; Tenofovir; Hepatitis B virus; Chronic hepatitis B

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VERTICAL TRANSMISSION OF HEPATITIS B VIRUS

It is estimated that almost 50% of the cases of chronic hepatitis B virus (HBV) infection result from vertical transmission or are acquired in early childhood, especially in endemic areas[1]. The prevalence of chronic HBV infection in pregnant women reflects that in the general population[2]. About 5% of mothers worldwide are chronic HBV carriers[3]; ranging from 0.6% in low-endemic regions to > 20% in high-endemic areas in the Far East and Africa[4,5]. The prevalence of HBeAg in pregnant HBV-positive women exceeds 50% in some high-endemic regions[5].

Mother-to-child transmission (MTCT, or vertical transmission) of HBV is one of the most important causes of chronic HBV infection[6] and is the most common mode of transmission worldwide. Maternal screening programs and universal active and passive immunoprophylaxis of

newborn have reduced dramatically the HBV transmission rates by 95%[7]. However, vertical transmission is still responsible for a significant number of cases of chronic infection[8] and remains a serious problem. MTCT can occur prenatally, during delivery, or postpartum. HBV is found in amniotic fluid, breast milk, vaginal fluids, cord blood and infant gastric content[9,10].

A large number of vertically transmitted cases occur intrapartum due to possible transfusion of the mother's blood to the fetus during contractions, as a consequence of membrane rupture, and *via* direct contact of the fetus with infected secretions, blood or other fluids from the maternal genital tract[11]. The risk of intrauterine infection is relatively low because the fetus is protected from HBV by the placenta. However, reported vaccination failures imply *in utero* transmission especially in high-risk groups (highly viremic and/or HBeAg-positive mothers)[12,13]. Furthermore, the risk is related to the presence of HBV DNA in the placenta[14] and to maternal viremia[15], which supports an association between maternal HBV load during pregnancy and the risk of transmission to the baby.

Despite successful screening and vaccination programs, high maternal HBV DNA is correlated with perinatal transmission. Wiseman *et al*[16] have shown a transmission rate of 8.5% for infants born to mothers with virus levels > 8 $\log_{10}$ copies/mL and no transmission below this cut-off. We need additional studies to assess the potential risk reduction associated with treatment of high maternal viremia during pregnancy. A study from India[17] has found that maternal viral load > 1.5×10^5 copies/mL is associated with intrauterine transmission. This presumes that nucleos(t)ide therapy during the third trimester with lamivudine (greater experience; FDA Category C) or tenofovir and telbivudine (Category B) might be beneficial. All these data concern prevention of intrauterine and perinatal transmission in mothers with HBeAg-positive chronic hepatitis and/or high titers of HBV DNA.

Some questions arise regarding breastfeeding in cases of chronic hepatitis B. Firstly, most studies that have been concerned with vertical or early childhood transmission have not reported breastfeeding rates, or if they have, the data are still the subject of debate. Secondly, the nucleoside analogues are likely to pass into breast milk to some degree. We have not established a policy for what to do in the case of nucleos(t)ide prevention in mothers who chose to breast feed. Thirdly, we have to measure the risk of breast-milk transmission in low-income individuals and regions with uncertain, unacceptable, unfeasible, and unsafe water supplies, or replacement feeding.

Recent studies have demonstrated the short- and long-term benefits of breastfeeding both for mothers and children. Breastfeeding, especially if exclusive and prolonged, leads to significant reduction in hospitalization rates for gastroenteritis, respiratory infections, and sepsis in the early months of life[18]. The benefits for low-resource countries are even greater because breastfeeding is related to better infant and childhood survival[19]. Exclusive breastfeeding for 6 mo, followed by continued breastfeeding at least to 12 mo, could prevent 1 301 000 deaths or 13% of all child deaths under 5 years of age in a hypothetical year[20]. New findings have emerged for older children, which support the role of prolonged breastfeeding in their cognitive functions[21]. A gene related to neuronal growth that depends for its effects on breastfeeding has been found recently. Individuals who carry at least one copy of this gene have higher IQ scores, but only if they have been breast-fed[22].

For older children and adults, long-term effects most probably include a possible impact of breastfeeding on cholesterol levels, body mass index, obesity and type 2 diabetes[23-25].

The benefits for breastfeeding mothers have been well described. Shorter recovery and oxytocin-stimulated uterus contraction prevents anemia. Lactation-induced suppression of ovulation has contraceptive effect during the period of exclusive breastfeeding[26]. Lactating women seem to regain their pre-pregnant weight sooner, and in the long-term have reduced obesity risk. The risks of breast and ovarian cancer and osteoporosis are also decreased[27-29]. When considering breastfeeding, we cannot omit the positive emotions and close mother-to-infant contact.

Despite consistent global policies in support of breastfeeding for the general population and World Health Organization (WHO) recommendations, the debate regarding HBV-infected women is still open in some countries. Guo *et al*[30] recently have reported an embarrassing number of HBV-positive women who opted for bottle feeding because of concern about the risk of transmission of HBV *via* breast milk.

HBV IN BREAST MILK AND SAFETY OF BREASTFEEDING

WHO postulates that chronic HBV infection of the mother could not be an argument against breastfeeding. However, some researchers and many clinicians disapprove it based on the results of some studies that have investigated the content of viral markers in human milk. In the early 1970s, Linnemann *et al*[31] and Boxall *et al*[32] published data on HBsAg transmission in breast milk of chronically infected mothers. Later, other researchers found not only HBsAg, but also HBeAg and HBV DNA in breast milk. In addition, both colostral HBsAg and HBeAg titers correlate positively with the corresponding level in maternal blood[33]. HBV DNA was found in 81.25% of Chinese mothers if HBsAg and HBeAg were positive and in 45.24% if HBeAg was negative[34]. de Oliveira *et al*[35] have evaluated HBV DNA in first- and fourth day colostrum of 24 Brazilians before and after pasteurization and have not found a significant difference (75% *vs* 67%).

Several studies have reported that breastfeeding carries no additional risk that might lead to vertical transmission. Table 1 summarizes comparative surveys regarding the rate of MTCT according to breastfeeding (BF) or formula feeding (FF).

Although one could find limitations, these studies have failed to demonstrate differences in HBV transmission regarding feeding practices in early childhood. Even in cases of no active or passive prophylaxis, the risk of transmis-

Table 1 Safety of breastfeeding in case of chronic hepatitis B virus infection of mothers

Author	No. of infants	Population	Prophylaxis	Infected or failed seroconversion to antiHBs		*P*
				BF (%)	FF (%)	
Beasley *et al*[56]	147	USA, Taiwan (China)	No	53	60	NS
Tseng *et al*[57]	170	Hong Kong (China)	HBIG + Vx	7	6	NS
de Martino *et al*[58]	85	Italy	Vx	4.6	3.2	NS
Hill *et al*[59]	369	USA	HBIG + Vx	0	3	0.06

BF: Breastfeeding; FF: Formula feeding; HBIG: Hepatitis B immune globulin; NS: Nonsignificant.

sion from HBV-positive mothers to their breastfed infants is at least equal.

WHAT COULD BE THE POSSIBLE EXPLANATION?

Beyond HBV infection, many studies have shown considerable differences between breast-fed and formula-fed infants, in spite of the notable progress in the composition of infant formulas. Breast milk provides a number of bioactive proteins that have different physiological activities. Lactoferrin is a major human milk protein with bacteriostatic (*Enterobacter sakazaki*[36]) and bactericidal activity (*Vibrio cholerae*[37]). It has antiviral activity against hepatitis C virus, adenovirus, cytomegalovirus, herpes simplex virus, rotavirus, adenovirus and human immunodeficiency virus (HIV)[38,39]. Recently, it has been found that lactoferrin and iron- and zinc-saturated lactoferrin significantly inhibit the amplification of HBV DNA in a dose-dependent manner in HBV-infected HepG2 cells[40].

There have not been sufficient studies that can even partially explain the possible effect of breastfeeding on eventual prevention of MTCT of HBV. However, there have been some discussions about the benefits of exclusive breastfeeding for HIV transmission. Inflammation or activation within the infant gut as a result of introduction of foreign antigens, contaminants and pathogens could activate probable mechanisms that facilitate viral transmission[41,42]. Small changes in the rate of suckling or non-exclusive breastfeeding could be associated with milk stasis and breast engorgement. If not reversed in a short time, the epithelial permeability might increase (leaky tight junctions)[43]. This phenomenon allows more efficient paracellular transfer of HIV and increased HIV RNA in breast milk[44,45]. Thus, irregular or non-exclusive breastfeeding might contribute to increased infectivity of human milk. It remains unclear if the situation with HBV is similar and could be a subject of future research. This issue is of considerable importance for high-prevalence regions with low social standards where promotion of exclusive breastfeeding is vital for child morbidity and mortality.

Research into probable HBV transmission mechanisms via breastfeeding is still open. The majority of studies have not measured maternal viral load quantitatively. Furthermore, it is difficult to draw any conclusion on the speculative correlation between the rate of MTCT and the duration of breastfeeding. The studies listed in Table 1 do not include randomly assigned cohorts, thus providing possible bias if some high-risk women decided to bottle-feed. Even the most recent study of Hill has evaluated a heterogeneous breastfeeding group and does not provide data for HBV DNA in mothers and infants (see the table for reference).

Finally, the American Academy of Pediatrics has recommended that HBV infection should not be considered as a contraindication to breastfeeding of infants who receive the approved hepatitis B immune globulin (HBIG) and HBV vaccine[46].

CONTROVERSIES IN NUCLEOS(T)IDE PROPHYLAXIS OF MTCT

Preemptive antiviral therapy[47] during pregnancy reflects an attempt to prevent intrauterine and perinatal transmission of HBV to newborn infants. However, some controversies remain, namely, when to start the therapy and for how long. The period immediately after birth is a time of treatment uncertainty in mothers who choose to breast-feed, because nucleoside analogues are likely to pass into the breast milk to some degree, and it is probably unwise to expose the child in this manner[47]. The pharmacokinetics of lamivudine are similar in patients with HIV or HBV and healthy volunteers. The absolute bioavailability of the drug is approximately 82% and 68% in adults and children, respectively. In pregnant women, concentrations in maternal serum, amniotic fluid, umbilical cord and neonatal serum are comparable, which indicates that the drug diffuses freely across the placenta[48]. Breast-milk to plasma concentration ratio has been determined at 2.96 for lamivudine, measured with high-performance liquid chromatography and tandem mass spectrometry[49]. Lamivudine has not been studied in HIV-negative nursing mothers who are being treated for hepatitis B infection, but the low doses used would not be expected to cause any serious adverse effects in breastfed infants. A recent study of maternal antiretroviral treatment from gestational week 34 to 6 mo postpartum has measured infant lamivudine concentrations at biologically significant concentrations. The median concentrations were 67 μg/L at delivery, 32 μg/L at week 2, 24 μg/L at week 6, 20 μg/L at week 14, and not measurable (< 16 μg/L) at week 24 postpartum[50]. Another study[51] has shown that neutropenia was 15.9% in the HAART-exposed infants at 1 mo of age compared to 3.7% in an unexposed group. Hematological toxicity was

transient and asymptomatic. The authors did not observe any difference in haematological and hepatic toxicity between breastfed and formula-fed infants from 2 to 6 mo postpartum[51]. Supported by the studies concerned with HIV transmission, we might reconsider stopping the preemptive antiviral therapy during BF if there is a high risk of HBV hepatitis flare. We also have to keep in mind the possible selection of resistant strains in case of suboptimal dosage in infected infants and the risk of adverse events.

After tenofovir had been studied in humans, it was classified by the US FDA in group B, thus presenting another treatment option during pregnancy. There are still no data to elucidate its transfer and concentration in human milk. An animal study with two nursing rhesus macaques has found that tenofovir is transferred to breast milk, but the peak concentrations were approximately 2%-4% of those detected in serum, with milk area under curve values being approximately 20% of the serum values[52]. For breastfeeding mothers who are taking the orally bioavailable prodrug tenofovir disoproxil fumarate, breast milk is expected to contain almost exclusively the parental compound tenofovir. It exhibits low oral bioavailability in animals and is expected to show low oral bioavailability after ingestion by nursing animals[53]. The small amounts of tenofovir in the milk are also very unlikely to select for resistance in already infected infants, thus preserving future treatment options[52]. To the best of our knowledge, a relevant study regarding drug levels in human breast milk and possible effects in breastfed infants has still not been published.

Breastfeeding seems not interfere with the immune response to the HBV vaccine. Wang *et al*[54] have followed up 230 infants for 1 year to assess the influence of breastfeeding on the efficacy of hepatitis B immunoprophylaxis. The rate of anti-HBs was 89.9% in the breastfed, compared to 73.2% in formula-fed infants among those that received HBV vaccine alone. In those who received a combination of HBV vaccine and HBIG, the anti-HBs levels were found to be similar (90.9% *vs* 90.3%).

When we compare inexpensive breastfeeding to formula feeding, we always have to remember the disturbing phenomenon of current industry practices. Bekelman *et al*[55] have confirmed the "sponsorship bias" in pharmaceutical research; their meta-analysis found industry sponsorship was associated with an OR of 3.6 (95% CI: 2.63-4.91) in favor of a pro-industry conclusion.

Finally, we encourage further studies to investigate urgently some hot topics in breastfeeding and HBV infection. These include the long-term follow-up of breastmilk HBV concentrations and correlation with serum viral load; the nucleos(t)ide analogues concentrations in breast milk in mothers with chronic HBV infection; the safety of tenofovir during pregnancy and lactation in chronic hepatitis B; and not least, the difference in viral load in the milk in exclusive and nonexclusive breastfeeding.

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