A disappearing vertical infection: will hepatitis B be a forgotten disease in children?

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The major transmission route of hepatitis B virus (HBV) is perinatal, especially during delivery in endemic areas. To decrease the prevalence of and complications associated with chronic hepatitis B, universal vaccination and maternal screening for hepatitis B serum antigen (HBsAg) are essential. Almost 5% of newborn infants are inadequately protected by current immunoprophylactic measures, and this figure may rise to 50% if prophylaxis is poor or the maternal HBV DNA load is high (> 10^7 IU/mL) [1].

In 2002, the Ministry of Health and Welfare and the Korea Centers for Disease Control and Prevention (KCDC) launched the Hepatitis B Perinatal Transmission Prevention Program (HBPTPP), which seeks to prevent vertical HBV infection. One program component is screening of all pregnant females for HBsAg. Prophylaxis (which is free) consists of hepatitis B immunoglobulin (HBIG, 0.5 mL) and recombinant HBsAg (10 μg). Infants of HBsAg-positive mothers are vaccinated within the first 12 hours after birth. Screening for HBsAg and anti-HB antibodies occurs 9 to 15 months after birth, and neonates with inappropriately low levels of anti-HB antibodies are reimmunized. In all, 161,187 newborn infants were at risk of perinatal infection between 2002 and 2012, of whom 156,290 (96.0%) were registered with the program; all medical costs were covered. The rate of failure of HBV immunoprophylaxis was ~3%; the program is thus highly effective [2]. The level of HBsAg-positivity in preschool children fell to 0.9% in 1995, thanks to universal vaccination, and further decreased to 0.2% in 2007 because of the success of the HBPTPP [1].

The rate of HBsAg-positivity among pregnant females in Korea was 3.4% in 1995, and did not decrease dramatically thereafter, being 3.2% in 2006 [1]. Recently, the Korea National Health and Nutrition Examination Survey compared data from 1998 (9,771 subjects) and 2009 (8,304 subjects), HBsAg seroprevalence decreased in this interval, especially among children and young adults. The rate was 2.2% in 1988, but only 0.3% in 2009 (and 0.1% in 2011, according to the KCDC) in those 10 to 19 years of age. In females of childbearing age (20 to 29 years), the figures were 5.4% and 2.5% in 1998 and 2006, respectively. In those 30 to 39 years of age, the figures were 6.1% and 4.3% [3]. It is expected that the HBsAg seroprevalence frequency of newborns will be less than 0.01% in 2020 to 2030, because a universal vaccination program and the HBPTPP were launched in 1995 and 2002, respectively. Kim et

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al. [4] found that the HBeAg-positivity rate among HBsAg-positive pregnant females was 37.7%.

Prophylaxis in the form of HBIG given immediately after delivery is of the utmost importance, as is vaccination against hepatitis B. HBV transmitted during delivery infects the newborn's liver and replicates exponentially. Thus, HBIG prophylaxis is absolutely essential to prevent HBV replication, especially if the maternal HBV load is high. However, HBIG does not prevent development of occult HBV infection if the maternal viral load is above a certain level [5].

The route of vertical infection is assumed to be microtransfusion via the placenta during delivery; or to be intrauterine transmission if either threatened abortion or threatened preterm labor (or both) has occurred during pregnancy [6]. Infection via swallowing of contaminated maternal blood was once thought to be a possible route of transmission. However, evidence is lacking. Systemic infection cannot occur via direct invasion of HBV through intact skin or the gastrointestinal mucosa. Intrapartum transmission of HBV is thought to be linked to placental microtransfusion caused by the separation of placental villi during the uterine contractions accompanying delivery. The human immunodeficiency virus is transmitted in this manner [7-9]. Intrauterine infection may occur even in early pregnancy via transcytosis of HBV across a trophoblastic barrier, especially in case of threatened abortion in pregnant females with high HBV loads, in whom HBV is detectable in the villous capillary endothelial cells of the placenta [10-12].

Factors associated with immunoprophylaxis failure may be subdivided into vaccine, host, and virus-related components. Vaccination-associated components are delays in administration of HBIG and the first dose of vaccine, site of injection (buttock), the use of short needles, inappropriate storage (freezing) of vaccine, and suboptimal vaccination. Host factors are any form of immunocompromise (including prematurity), reactivation of HBV from other cells, and genetic determinants of non-response to vaccination. Virus factors are high HBV concentrations in maternal blood, in utero infection via placental leakage, prolonged labor, a history of preterm labor, and vaccine-breakthrough mutations [13]. Critically, higher maternal HBV DNA levels combined with detectable HBV DNA in cord blood is the most important predictor of vertical infection and is associated with higher rates of immunoprophylaxis failure [14-16]. Among-country failure rates may be influenced by various factors, principally the maternal hepatitis B e antigen (HBeAg)-positivity rate, the HBV DNA level, and the timeliness (or not) of postnatal HBIG administration. The HBV viral load in pregnant females may be higher in East Asian than Western countries.

In the current issue of this journal, Kim et al. [4] report that no case of vertical infection was recorded between 2005 and 2012, whereas the rate was 4.0% (4/100) between 2002 and 2004. Although HBIG was indeed given to all neonates immediately after birth in 2005 to 2012, the perfect prophylaxis rate over an 8-year period is truly remarkable. It might be hypothesized that maternal antiviral prophylaxis during the last trimester had been randomly done individually, although HBeAg-positive mothers had not previously received any antiviral treatment. This assumption could not be tested because maternal HBV DNA levels immediately prior to delivery were not measured. Antiviral prophylaxis for HBsAg-positive pregnant females has become increasingly available since the early 2000s in many Korean hospitals, although the treatment was not covered by medical insurance. In addition, the cited authors did not mention when infants were tested for HBsAg; newborn infants have higher levels of HBsAg positivity than do those aged 9 to 15 months. It is notable that 56/308 infants (18.2%) were lost to follow-up; they may include > 1.6% of (all) infants that were HBsAg-positive. Thus, it is difficult to believe the perfect results obtained between 2005 and 2012. Nevertheless, a postnatal prophylaxis rate above 98% is outstanding. Immediate treatment with HBIG clearly works, and the data indicate that HBV may indeed be eradicated from children in the future.

Nucleos(t)ide analogs (lamivudine, telbivudine, and tenofovir) may be given in the third trimester to suppress viral replication in HBsAg-positive pregnant females with high HBV DNA loads. This should reduce maternal HBV viremia at delivery, in turn reducing the risk of vertical infection via placental microtransfusion. However, risks remain [17-20]. If the maternal HB viral load is > 6 to 7 $\log_{10}$ IU/mL, antiviral prophylaxis should commence in the third trimester, continue to

the day of delivery, and be of at least 1 to 3 months' duration [21,22]. The target HBV DNA level should be lower than 6 $\log_{10}$ IU/mL. Maternal monitoring is necessary to treat any possible exacerbation of alanine aminotransferase after delivery [23].

Cesarean section (CS) may reduce the risk of vertical transmission if a difficult delivery is expected; placental microtransfusion increases if delivery is prolonged. However, the available data differ among several studies, and CS is not recommended if a normal spontaneous vaginal delivery is expected [24-26]. However, an elective CS may be effective in highly viremic mothers, although emergent CS did not differ from vaginal delivery in terms of reducing vertical transmission [27]. The data suggest that perinatal mother-to-infant transmission does not involve contact with maternal blood or contaminated amniotic fluid during delivery.

HBV is present in breast milk [28]; however, breast-feeding is not a risk factor for perinatal transmission. Thus, breast-feeding should be recommended, because breast milk contains very high levels of useful immunological and antimicrobial materials. Several studies worldwide have shown that formula feeding does not reduce the residual infection rate in the context of appropriate postnatal prophylaxis [26,29-31]. In a recent Chinese study, failure of prophylaxis was higher in formula-fed than breast-fed infants regardless of HBV DNA levels in breast milk [26]. Infected infants on breast-feeding are assumed to be infected not by breast milk, but by placental leakage during or before delivery. Nipple cracking with bleeding is common during lactation, but is not a contra-indication for breast-feeding, because maternal blood is diluted in the neonatal gut and it is difficult to accept that HBV can invade the normal gastrointestinal mucosa (which is in continuous motion). Circulating anti-HB antibodies present after HBIG treatment can be persistently detected for over 2 months, and anti-HB antibodies are produced by the infant during this period. Additional HB vaccination at 2 months after birth has been reported to be effective in Thailand, where HBIG is not available.

To further inhibit vertical transmission, the KCDC and the Korean Pediatric Society (KPA) publish annual guidelines on prevention of hepatitis. The KPA and the Korean Association for Study of the Liver also educate healthcare professionals.

The importance of antenatal screening must be emphasized continuously, and should include assessment of maternal HBeAg status and measurement of HBV DNA level if the HBsAg test is positive. Also, in emergency units, prophylaxis must be given within 12 hours of delivery. Further, as international marriages between immigrant females (including refugees from North Korea) and Korean males may increase the risk of perinatal transmission, it is necessary to develop an HBPTPP and educational programs for immigrants. A universal vaccination program has been successfully launched in North Korea, sponsored by an international nongovernmental organization. Continuous support, including an HBPTPP, is needed, to ensure that infections in North Korean children do not rewind the success clock of HBPTPP after the Republic of Korea and North Korea are reunited.

Infants born with HBsAg because of prophylactic failure should be appropriately monitored and managed. Regular follow-up is required to determine the appropriate treatment time. Conversion to early immune clearance phase is accelerated in children over the age of 12 years [32]. Active treatment should be considered upon onset of the immune clearance phase, to ensure that the optimal treatment time is not missed [33]. Although children respond to treatment better than do adults, emerging antiviral resistance is difficult to manage because the newer antiviral agents have not been approved for children with HBV infection [34-36]. Global studies on the safety and efficacy of potent antiviral agents with high genetic barrier in children are ongoing. Approval of entecavir and tenofovir as primary treatment options in children should be awaited in the meantime [33].

The dramatic decline of the HBsAg-positivity rate in children is an optimistic sign that HBV will be eradicated in children in the near future. Hepatitis B will die; the disease will not occur in the next generation of Korean children.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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