論　文　内　容　要　旨

Residual risk of mother-to-child transmission of HBV despite timely Hepatitis B vaccination: a major challenge to eliminate hepatitis B infection in Cambodia

（カンボジアにおけるＢ型肝炎ワクチン定期接種導入後にも残存している母子感染リスク：Ｂ型肝炎ウイルス撲滅に向けた課題と考察）

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【Background】

Although the World Health Organization (WHO) calls for the elimination of viral hepatitis as a public health threat by 2030, the existence of mother-to-child transmission (MTCT) of hepatitis B virus (HBV) in intermediate and high endemic areas remains challenging. By 2017 nationwide study, Cambodia has reportedly intermediate endemicity with 4.39% of HBsAg prevalence among women of childbearing age (Vaccine, 2019). Though the immunization of all infants with hepatitis B (HepB) vaccine aims to prevent perinatal transmission, WHO recommends antiviral prophylaxis for pregnant women at high risk of transmitting HBV (HBsAg-positive with HBV viral load >200 000 IU/mL or $>10^6$ copies/mL, or HBeAg positive) as additional strategy to prevent HBV MTCT.

In Cambodia, the nationwide vaccination program against HBV infection started in 2005 with administration of HepB vaccine birth dose (within 24 hours), followed by 3 booster doses at 6, 10, and 14 weeks of age. The vaccine coverage increased over time and as of 2020, the HepB birth dose coverage was 90% nationwide. Other preventive strategies such as HBsAg screening during antenatal care and antiviral prophylaxis are adopted in 2021 but not yet implemented nationwide, while hepatitis B immune Globulin (HBIG) is optional if available and affordable. This situation urges to evaluate the HBV MTCT in Cambodia. Therefore, this study aimed to investigate the prevalence of HBsAg among pregnant women and to ascertain if MTCT of HBV is occurring in Cambodia. The findings obtained through this study will contribute to improving prevention strategies against HBV MTCT in Cambodia.

【Methods】

Between February 2020 and December 2021, a longitudinal study was conducted among pregnant women attending antenatal care at three hospitals in Siem Reap Province, Cambodia. The study was divided into 2 parts (study-1 and study-2).

In study-1, pregnant women were screened for HBsAg by rapid test (Abbott Determine™, USA) and their serum samples were collected for further analysis. Questionnaires were used to collect socio-demographic data. By sample size calculation, 1,500 pregnant women were required for HBsAg screening.

All HBsAg positive pregnant women and one-fourth of HBsAg negative pregnant women were invited to participate in study-2 for follow-up visits at delivery and 6 months later. At delivery, cord blood samples were collected. At 6-month follow-up, newborn babies were tested for HBsAg using rapid test; additionally, dried blood spot (DBS, Hemaspot™ Spot on Sciences, CA, USA) samples were taken for confirmatory test and further analysis.

All collected samples were shipped to Hiroshima University for laboratory analysis. HBV sero-markers were measured using a chemiluminescent enzyme immunoassay (CLEIA, Fujirebio, Japan). HBV DNA was quantified by Real Time PCR. Genome sequencing was performed for genotype identification and mutation analysis. Multivariable logistic regression was used to identify factors associated with HBsAg positivity in pregnant women.

【Results】

A total of 1,565 consenting pregnant women participated in study-1, with mean age of 28.3 ± 5.7 years old. The prevalence of HBsAg among pregnant women was 4.3% (67/1,565) with mean age of 29.4 ± 5.4 years old. Multivariable analysis indicated that pregnant women who received HepB vaccine were significantly associated with a lower risk of HBsAg positivity (AOR: 0.22, p=0.011). Of the 67

HBsAg positive pregnant women, 41.8% (28/67) were HBeAg positive and 28.4% (19/67) had a high viral load exceeded 10^6 copies/mL. Median viral load of HBeAg positive samples was significantly higher than that of HBeAg negative samples (HBeAg positive: 1 x 10^8 copies/mL, HBeAg negative: 4 x 10^3 copies/mL, $p<0.001$) and the viral load decreased by increasing age ($p=0.029$). Genotype was identified in 61 samples, with genotype C being predominant (68.9%, 42/61) followed by genotype B (31.1%, 19/61).

In study-2, out of 442 pregnant women (including 67 HBsAg positive) invited for follow-up, 145 (including 37 HBsAg positive) were enrolled, amongst whom 101 (including 17 HBsAg positive) delivered at study hospitals and 116 babies (including babies of 35 HBsAg positive mothers) who visited follow-up at their 6 months old were included in evaluating MTCT. HBsAg was detected in cord blood of 6 out of 17 babies born to HBsAg positive mothers. At 6-month follow-up, out of 35 babies born to HBsAg positive mothers (including 5 out of 6 babies with HBsAg positive cord blood), one baby was HBsAg positive resulting in 2.9% risk of HBV MTCT. None of 81 babies born to HBsAg negative mothers tested positive at 6 months old. All 116 babies received timely HepB birth dose and completed 3 booster doses except two babies born to HBsAg negative mothers missed their 3rd booster.

The HBsAg positive baby at 6 months old received timely HepB birth dose and 3 booster doses as well as HBIG; and no mutation was detected in "a" determinant region. The mother of the infected baby had a high HBV viral load of 1 x 10^9 copies/mL and was positive for HBeAg and had no history of antiviral treatment. Furthermore, the cord blood of this baby was HBsAg positive, so that the baby might be infected during pregnancy.

【Conclusion】

The results of this study showed an intermediate endemicity of HBV infection (4.3%) among pregnant women in Siem Reap of Cambodia, which is consistent with previous 2017 nationwide report (Vaccine, 2019). Among HBsAg positive pregnant women, 28.4% (19/67) had HBV viral load greater than 10^6 copies/mL, indicating a high risk of HBV MTCT. As Cambodia is now considering nationwide implementation of antiviral prophylaxis as recommended by the WHO for pregnant women at high risk for HBV MTCT, these findings can serve for health policy planning, enabling effective preparation and decision-making.

Although all 35 babies born to HBsAg positive mothers received a complete series of HepB vaccination, one baby tested positive for HBsAg at 6 months of age, resulting in a residual risk of HBV MTCT of 2.9%. The infection of the baby might have occurred during pregnancy (intrauterine infection), which could not be prevented by the vaccine administered at birth. To date, there is no specific intervention for preventing intrauterine infection of HBV. This situation underscores the need for further research on intrauterine infection of HBV and its prevention measure. However, perinatal transmission cannot be ruled out in this case. Therefore, in addition to the HepB vaccine, nationwide implementation of the updated (2021) guideline, which includes HBsAg screening among pregnant women at antenatal care and administering antiviral prophylaxis for those at high risk of HBV MTCT, should be considered.

Overall, this study provided valuable insights into the prevalence of HBV infection among pregnant women and the proportion of those at higher risk of MTCT. Furthermore, this study revealed the existence of a residual risk of HBV MTCT within Cambodia's current prevention measure. These findings are beneficial for Cambodia in improving preventive strategies against HBV MTCT.