**Scientific Research Process**

A retrospective study to determine risk factors with a specific focus on the impact of HBV DNA level for vertical transmission of chronic hepatitis B (HBV) infection was designed in collaboration between Stanford University and the Immunization Branch of the California Department of Public Health.

The study aim was to explore risk factors for perinatal transmission of chronic HBV infection for infants born to HBsAg positive women in California. Our hypothesis was that infants born to mothers with high HBV DNA level would be at higher risk for perinatal transmission despite receiving appropriate post-exposure prophylaxis.

Eligible infants born to HBsAg positive women in California between January 1, 2005 and December 31, 2011 whose HBV infection status was known via PVST were identified from the Perinatal Hepatitis B Prevention Project (PHPP) database . Demographic data, laboratory results, times of HBIG and HBV vaccine administration at birth and completion of the HBV vaccine series, and PVST results were also recorded. Definition of PEP error was based on ACIP guidelines of appropriate administration of HBIG, HBV birth dose and completion of the hepatitis B vaccine series. Birth certificate data on maternal race and ethnicity, birthplace, education level and insurance status during pregnancy and details about the delivery were obtained for all infants and matched to PHPP records.

Laboratory data, specifically HBeAg and HBV DNA, are rarely reported to PHPP. Therefore test results for women of childbearing age 14 to 45 years between January 1, 2005 and December 31, 2011 were requested from three large reference laboratories that serve most patients in California: Quest Diagnostics (Madison, NJ, USA), LabCorp (Burlington, NC, USA), and ARUP Laboratories (Salt Lake City, Utah, USA). These laboratory results were matched to PHPP records by mother’s name, date of birth, and proximity of mother’s residence zip code to the ordering provider’s zip code. For all infected cases, maternal prenatal care providers were contacted to obtain any additional HBV DNA and HBeAg results that were available.   
A case control analysis was undertaken to compare infants with positive HBsAg results indicating perinatal infection and control infants with negative HBsAg results. A statistical plan was created and focused on our limited sample size of infected infants whose mothers had available HBV DNA results (27 infants). We set a predefined exposure of HBV DNA > 2x107 IU/ml given prior studies suggesting high viral DNA infers a higher risk for perinatal transmission. A 5:1 ratio of cases to controls and two-sided confidence level of 95% was used for more than 95% power to detect an odds ratio of greater than 50. Multivariate analysis was restricted to cases and controls with complete maternal HBV DNA results.

Our study is the largest single state sample size of perinatal transmission completed outside of Asia. In California, PEP and vaccination are widely used and highly effective to prevent perinatal HBV transmission with an overall perinatal transmission rate of only 1.1%. The incomplete PVST rate may underestimate the burden of pediatric chronic HBV infection in California and is a call to action for pediatricians caring for these at-risk infants. Our study demonstrates that infants of mothers with high HBV DNA level of ≥ 2x107 IU/mL are clearly at an increased risk of perinatal transmission. Yet, we found very few pregnant women with maternal HBV DNA levels, limiting the ability for providers to risk stratify these women for possible anti-viral therapy to prevent perinatal transmission.