IRB Protocol

Post-Partum Follow-Up of Women Who Are HBsAg Positive on Antenatal Screening

A. Study Purpose and Rationale

Hepatitis B Virus (HBV) infection is major public health concern and a cause of significant morbidity and mortality. In the United States, an estimated 1.25 million individuals are HBV carriers and 73, 000 new cases of HBV infection are reported annually.[1, 2] Each year approximately 600,000 individuals die of complications such as acute liver failure, cirrhosis, and hepatocellular carcinoma (HCC).[3] It is estimated that 23, 000 HBsAg-positive women give birth every year.[4] The prevalence of hepatitis B surface antigen (HBsAg) positive pregnant individuals varies with geographic location, race and ethnicity. As expected in the US, the highest rate (6%) is in Asian women. The rates in black, white and Hispanic women are 1, 0.6 and 0.14% respectively.[5]

There are well established guidelines for the screening of all pregnant women for Hepatitis B Virus (HBV) within the first trimester. Recent estimates indicate that more than 95% of pregnant women are tested for HBsAg, and case management has been effective in ensuring high levels of initiation and completion of post-exposure immunoprophylaxis among identified infants born to HBsAg positive women.[6] The utilization of passive–active immunization with HBV vaccine and HBIG administered 12–24 h after birth, followed by completion of a three-dose vaccine series, have been shown to be 85–95% effective in preventing acute and chronic HBV infection in infants born to women who are positive for both HBsAg and HBeAg.[7,8] Hepatitis B vaccine has been successfully integrated into the childhood vaccine schedule, and infant vaccine coverage levels are now equivalent to those of other vaccines in the childhood schedule.

Nevertheless, the implications of detecting an HBV-infected pregnant woman go beyond prevention of transmission of infection to the neonate. There is data to suggest that alterations in the immune system that occur during and after pregnancy may provoke acute flares of chronic hepatitis B during the peri-partum period.[8,9] There appears to be a shift in the TH1–TH2 balance towards a TH2 response with increased amounts of regulatory T cells, which also seem to play a role in chronic hepatitis B infection, contributing to an inadequate immune response against the virus allowing for tolerance against the hepatitis B virus during pregnancy.[8,9] All these changes in the immune status recover after delivery and the immune system fully restores its function. Therefore it is hypothesized that this reactivation of the immune system is responsible for a post-pregnancy increase in liver disease activity.[9] It is thus imperative to monitor HBV-infected women closely for several months after delivery for hepatitis flares and seroconversion.[5]

It appears that there is currently a paucity of literature examining outcomes and degree of follow-up of HBsAg positive women in the post-partum period. In fact, a review of the literature suggests that these women are infrequently the focus of HBV infection in pregnancy, with greater attention focused on the risks to the infant through maternal-fetal transmission. A UK study done by Orchard et. al,found that over 30% HBV positive women identified from pregnancy screening are not assessed in hepatology clinics.[10] Prenatal screening should serve not only to identify women at high risk for vertical transmission of HBV to her fetus, but to also enroll women in further care, identify her stage of chronic infection, manage liver disease (especially acute flares that commonly occur in the post-partum period) and initiate treatment or further screening for clinical complications.

Hypothesis
There is inadequate post-partum clinical and virological follow-up of women testing positive for HBV in the setting of antenatal screening

B. Study Design and Statistical Analysis

This is a retrospective chart review involving all pregnant women seen at Columbia University Medical Center who received prenatal testing between Jan 2006 and December 2009 and found to be HBsAg positive on screening. A total of 7,020 deliveries were performed during this time period. Among this cohort, 101 women were found to be HBsAg positive. Charts will be reviewed and assessed for an average follow-up period of 3 years. This review will require going through patient records to collect data points related to study outcomes.

The primary outcome will be whether or not the patient was followed up for further management of HBV infection via referral to a specialist with either a gastroenterologist or hepatologist. Hepatology appointments offered, attendance and subsequent management will recorded.

The secondary endpoint will be an evaluation of performance and values of serological and virological markers considered as standard of care in evaluation of liver disease, stage of chronic infection (LFTs, HBV DNA viral load, HBeAg/Ab), and further imaging.

Secondary analysis: Baseline demographic and epidemiological data will be collected. Further they will be assessed for correlation with degree of follow-up and degree of liver disease

Statistical analysis will be performed using a one-sample chi-square test for proportions to determine an 80% power at $p<0.05$. There is a predetermined sample size of 101 patients and thus Chi-square was used to determine effect size with a comparison proportion of 0.9. This number was determined arbitrarily based on the fact that it is an expectation that most women should receive standard of care when found to be HBsAg positive on prenatal screening. Based on these values we will be able to detect $p<0.8$ and $p>0.97$. Meaning that we will be able to detect a difference if the study prevalence of women who do not receive adequate follow-up is less than 80%. Descriptive statistics (mean, standard deviation, range) will be applied to evaluate baseline characteristics. Univariate analysis will be used to evaluate factors that influence the primary and secondary outcomes.

C. Study Procedure.

All information for this study will be collected through CUMC paper and electronic medical record review. The variables collected will include the following: gender, race/ethnicity, type of Health Insurance, age at time of pregnancy, laboratory tests performed within the prenatal period (including LFTs, HBV DNA level, HBeAg, HBeAb), post-partum laboratory results, post-partum clinic/hospital visits, radiologic Imaging (MRI, CT, US), treatment of virus.

D. Study Drugs

Not applicable

E. Medical Device.

Not applicable

F. Study Questionnaires

Not applicable

G. Study Subjects

This study will evaluate all adult women who have undergone HBV screening in the prenatal period and are found to be positive for HBsAg. Further, patients will be included in the study if they have medical records available for review in the post-partum period. Patients will be excluded if there is insufficient data and records in the 3-year period after giving birth.

H. Recruitment of Subjects

This is a retrospective chart review, patient charts and electronic medical record review will be performed at CUMC and thus no active recruitment will be involved.

I. Confidentiality of Study Data

Data will be protected by standard privacy mechanisms adopted by CUMC. Data collection will involve de-identification to adhere to confidentiality. All study information will be de-identified and coded to protect the rights and confidentiality of each individual patient. All collected data will be stored in a secure location, accessible only to study investigators.

J. Potential Conflict of Interest

Not applicable

K. Location of the Study

Patient chart and electronic medical record review and analysis will be performed at CUMC.

L. Potential Risks

The risks of this retrospective study are essentially limited to the risks associated with disclosure of PHI outside CUMC, something that can be easily avoided through the adequate confinement of patient identifiers to the research setting

M. Potential Benefits

As this is a retrospective chart review, there will be no benefit to the patients included in the analysis. However study results may yield improvement in future post-partum care of women found to be HBsAg positive on ante-natal screening and allow us to see how we can improve our clinic follow up services.

N. Alternative Therapies

No experimental therapies are involved in this protocol.

O. Compensation to Subjects

As this is a retrospective chart review no compensation will be provided to subjects.

P. Costs to Subjects

The subjects will not incur any costs as a result of participating in this study.

Q. Minors as Research Subjects

No minors will be included in this protocol.

R. Radiation or Radioactive Substances

No radiation or radioactive substances are involved in this protocol.

---

1. Centers for Disease Control and Prevention. Incidence of acute hepatitis B – United States, 1990–2002. *MMWR* 2004; 52: 1252–4.
2. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. *J Viral Hepatology* 2004; 11: 97–107
3. World Health Organization. Hepatitis B vaccines. *Wkly Epidemiol Rec* 2009;84:405-419.
4. Colin W. Shepard, Edgar P. Simard, Lyn Finelli, Anthony E. Fiore, and Beth P. Bell Hepatitis B Virus Infection: Epidemiology and Vaccination. *Epidemiol Rev* (2006) 28(1): 112-125
5. Jonas MM. Hepatitis B and pregnancy: an underestimated issue. *Liver International* 2009;29 (Suppl 1):133-139.
6. Centers for Disease Control and Prevention. A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States Recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: Immunization of Adults. *MMWR* 2006;55(No. RR-16):[1-2].
7. Andre FE, Zuckerman AJ. Review: protective efficacy of hepatitis B vaccines in neonates. *J Med Virol 1994*; 44: 144–51.
8. S. Sinha and M. Kumar. Pregnancy and chronic hepatitis B virus infection. *Hepatology Research* 2010; 40: 31–48
9. Ter Borg, M. J., W. F. Leemans, R. A. De Man, and H. L. A. Janssen. "Exacerbation of Chronic Hepatitis B Infection after Delivery." *Journal of Viral Hepatitis* 15 (2007): 37-41.
10. Orchard, P., A. Baxter, A. McEwan, S. D. Ryder, and M. W. James. "Transferring Care of Hepatitis B-infected Mothers from Obstetrics to Hepatology: Where Are the Barriers?" Gut 60.Suppl 1 (2011): A236.