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HEPATITIS B AND PREGNANCY

In this Issue...

Mother-to-child-transmission of hepatitis B remains a significant problem worldwide. In this issue, we review recent data from Asia that suggest hepatitis B e antigen (HBeAg) as a factor in perinatal transmission and its possible relationship to global immunoprophylaxis strategies and recommendations. Several studies over the last several years have looked at HBV transmission rates, even with appropriate vaccination and the role played by high maternal viremia in transmission. More recent studies have identified maternal viremia levels > 10^8 copies/mL as a risk factor, with transmission rates approaching 9% in these patients. These findings have led to therapeutic trials of oral antiviral agents for use in women with hepatitis B in pregnancy, specifically in the third trimester, in the hopes of reducing transmission rates in these highly viremic mothers. Other key issues related to pregnancy, including breastfeeding, are also addressed in a meta-analysis.

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- Assess hepatitis B virus (HBV) vaccination strategies
- Evaluate data on therapies used for the prevention of mother-to-child transmission (MTCT) of HBV

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- **Raymond T. Chung, MD,** has disclosed that he has received grants/research support from Gilead, Pfizer, Roche/Genentech, Merck, and Romark.

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THIS ISSUE

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Unlabeled/Unapproved Uses

The author has indicated that there will be references to unlabeled/unapproved uses of tenofovir and lamivudine in pregnancy in this presentation.

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COMMENTARY

Hepatitis B therapy has advanced significantly over the past decade with the use of antiviral therapies that can suppress the virus and mitigate histologic injury without long-term viral resistance. The reduction in rates of mother-to-child-transmission of HBV infection is still attributed predominantly to the safe, efficacious, and widely available HBV vaccine, and the studies have shown that with the use of the vaccine, approximately 90% of infants born to HBV- infected mothers will be protected from getting the virus.[1]

The remaining 10% of infants, likely born to mothers with high levels of viremia , as seen in the papers presented here, have either experienced vaccine failure or are exposed in utero to the virus. Data presented here suggest that antiviral therapy with lamivudine,

tenofovir, or telbivudine during pregnancy may reduce maternal viral levels and reduce the risk of transmission. Although data is still limited by the paucity of high-quality, randomized, controlled trials in this population, evidence seems to suggest that treatment with antivirals may be an effective strategy.

Once these high-risk infants are born, immediate administration of the HBV vaccine plus hepatitis B immune globulin (HBIg) should be carried out and completed according to protocol, although it is possible that HBeAg-negative patients may not require the addition of HBIg. Breastfeeding in this population has been controversial, but numerous studies, including the meta-analysis presented herein, reaffirm the safety and low risk for HBV transmission associated with breastfeeding, which has proven health benefits among newborn infants.

Safety should be considered of utmost concern in this sensitive population. The Antiretroviral Pregnancy Registry, which comprises mainly patients with human immunodeficiency virus (HIV), is limited both in its scope and by its self-reported, short-term nature, but it does release findings on the safety of these HBV agents.

When contemplating the use of antiviral therapy, the clinician must always separate the issue of treatment for the mother's benefit from treatment to prevent disease transmission. Treatment strictly for the mother's benefit is rarely needed in the short term, so therapy can likely be deferred until after pregnancy. Treatment to reduce the risk of mother-to-child transmission must be undertaken with consideration of the available data, along with the mother's clear understanding of the associated risks and benefits.

Commentary References

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MATERNAL SCREENING AND UNIVERSAL IMMUNIZATION FOR THE PREVENTION OF MOTHER-TO-INFANT HBV TRANSMISSION

Chen HL, Lin LH, Hu FC, et al. **Effects of maternal screening and universal immunization to prevent mother-to-infant transmission of HBV.** *Gastroenterology*. 2011 Dec 22. [Epub ahead of print] .

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Mother-to-child-transmission has been and remains worldwide one of the most common modes of spreading chronic HBV infection. The HBV vaccine was made widely available in 1982, and since that time, acute hepatitis B infection has declined by 94% among children and adolescents in the United States, attributed mainly to implementation of vaccination protocols.[1] It had been established that mothers who are HBeAg-positive have a higher risk for HBV transmission to their unborn infant than do mothers who are HBeAg-negative (70% to 90% vs. < 10%, respectively, without prophylaxis).[2] This is due in part to higher HBV DNA levels in the HBeAg-positive woman. The Advisory Committee on Immunization Practices currently recommends that any infant born to a mother with hepatitis B receive HBV vaccination plus HBIg within 12 hours of birth, and complete the three-dose vaccination series by six months of age.[3] With this strategy of immunoprophylaxis, 85% to 95% of infants born to hepatitis B surface antigen (HBsAg)–positive/HBeAg-positive mothers subsequently become HBV- negative.[3] The use of HBIg in all HBV-positive mothers is still controversial, with HBIg administration either difficult or cost-prohibitive in many areas of high disease prevalence.

The current review by Chen and colleagues analyzed data on the use of HBIg in 2356 children born to HBsAg-positive mothers. HBIg and HBV vaccination were administered to all mothers who were prenatally determined to be HBsAg-positive/HBeAg-positive (n = 583). In mothers who were HBsAg-positive/HBeAg-negative, HBV vaccine was

administered, but HBIg was not given unless by parental choice. Of those who were HBeAg-negative, 1050 of 1773 mothers were not given HBIg, whereas 723 did receive HBIg. The overall HBV infection rate in this large cohort was 2.5%, with the HBeAg-positive group having a transmission rate of 9.26%, vs. 0.23% in HBeAg-negative mothers. In the HBeAg-negative group, there was no statistical significance in transmission between those who had received the HBV vaccine plus HBIg and those who had received only the HBV vaccine at birth. Antibodies against the hepatitis B core antigen (anti-HBc) were also examined in this study, with rates of positive anti-HBc also much higher in the HBeAg-positive group than in the HBeAg-negative group (16.7% vs. 1.58%, respectively), suggesting that infection and subsequent seroconversion occurred much more frequently.

This analysis confirms previous smaller studies that demonstrated higher rates of transmission in HBeAg positive mothers. More important, however, in the HBeAg- negative cohort, HBIg did not appear to affect disease transmission rates, which were low overall. Interestingly, HBV genotyping was compared between mother-infant pairs and surface mutants were found in 32% of 25 infants tested, suggesting HBIg immune pressure on selection of viral strains. One case of fulminant HBV was reported in an infant born to a mother with HBeAg-negative disease. The implications of this study may be important in the worldwide development of testing and vaccination strategies with regard to global prevention of HBV infection.

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HBV PERINATAL TRANSMISSION AMONG MOTHERS WITH HIGH VIRAL LOADS

Wiseman E, Fraser MA, Holden S, et al. **Perinatal transmission of hepatitis B virus: an Australian experience.** *Med J Aust*. 2009;190(9):489-492.

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With the widely available HBV vaccine, mother-to-child transmission of acute and chronic HBV infection has been dramatically reduced, with the impact being achieved even with respect to associated hepatocellular carcinoma rate reductions.[1] As noted in the previous article, determination of HBV perinatal transmission risk has been performed mainly via HBsAg and HBeAg status. More recently, however, the use of quantitative HBV DNA in clinical practice has led to the study of HBV DNA levels as a predictor of perinatal transmission, specifically among HBeAg-positive women, who are expected to have higher HBV DNA levels. A 10-year meta-analysis from the Netherlands examined 705 newborns born to HBsAg-positive mothers between 1982 and 1989.[2] In this study; the only factor that significantly affected the protective efficacy rate of passive-active immunoprophylaxis was maternal HBV DNA level. In this earlier analysis, albeit with different HBV DNA assays than those currently used, 100% protective efficacy was achieved in women with maternal HBV DNA levels < 150 pg/mL-1. [2] In contrast, the protective efficacy rate was only 68% if the maternal HBV DNA level was > 150 pg/mL-1. 2 Eight of the 705 children from this meta-analysis became HBsAg- positive within the first year of life. Compared with noninfected responders to standard passive-active immunoprophylaxis, 7 of the 8 children were noted to have had significantly higher maternal HBV DNA levels before birth. This prompted the authors of the study to conclude that the extent of viremia was likely to play a large role in the failure of standard immunoprophylaxis.[2] In 1989, Ip and associates

reported similar results, in which infants born to mothers with HBV DNA levels < 150 pg/mL-1 were all HBsAg-negative at 12 months, whereas those born to mothers with HBV DNA levels > 150 IU/mL had a 25% to 50% risk for developing chronic HBV infection (CHB), regardless of immunization status.[3]

More recently, the review by Wiseman et al[4] discusses one of the largest studies of this kind in a prospective, observational study of perinatal HBV transmission in Australia conducted between 2002 and 2008. Pregnant women who tested positive for HBsAg and their babies, all of whom were offered standard HBV vaccine plus HBIg, were followed during and after delivery. In this study, of 313 mother-infant pairs who were evaluated, 68% were HBV DNA-positive and 29% were HBeAg-positive. A total of 138 of the 213 babies born to HBV DNA-positive mothers (138/213) were tested for HBsAg at 9 months, and four cases of HBV transmission were identified. In those four infants, the mothers were all HBeAg-positive, and all the mothers had high viremia levels (> 10^8 copies/mL).

The overall transmission rates were 3% in infants born to HBV DNA-positive mothers, 7% in those born to HBeAg-positive mothers, and 9% in those whose mothers had high viremia levels (> 10^8 copies/mL).

This study and the preceding ones suggest that immunoprophylaxis failures occur at higher rates in infants whose mothers have high levels of viremia. With observed rates of MTCT approaching 10% in this subpopulation, the concept of antiviral therapy during pregnancy has subsequently emerged.

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LAMIVUDINE USE IN LATE PREGNANCY FOR THE PREVENTION OF PERINATAL HBV TRANSMISSION

Xu WM, Cui YT, Wang L, et al. **Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multicentre, randomized, double-blind, placebo-controlled study.** *J Viral Hepat*. 2009;16(2):94-103.

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Given data regarding high maternal viremia levels and transmission of HBV and experience with prevention of HIV transmission with antiviral therapy, treating HBsAg-positive pregnant women was considered a logical therapeutic option to reduce viral transmission and possibly lower disease transmission rates. Lamivudine appeared to be the most viable candidate, as data regarding use of that agent in pregnancy were available from the treatment of HIV-infected pregnant women. Since no changes in drug pharmacokinetics attributable to pregnancy are observed with the use of lamivudine, it appears as if the agent can be used in pregnancy without any dosing adjustments.

van Zonneveld and colleagues analyzed eight pregnant women with HBV DNA levels > 1.2 x 10^9 copies/mL who were treated with lamivudine 150 mg/day beginning at week 34 of pregnancy through delivery.[1] The infants received HBIg at birth and completed the HBV vaccine series. Among these treated women, the median drop in HBV DNA levels was 98.9%. Of the eight infants born to treated mothers, four were HBsAg-positive at birth, but

only one remained positive at 1 year of life. The authors compared this treatment cohort with a historical cohort and found that with the use of lamivudine, the risk for perinatal transmission decreased by a factor of 2.9. No adverse effects were observed in mothers or infants.[1]

In the current review, which is one of the only published randomized, double-blind studies conducted in pregnant HBV women with HBV, Xu and colleagues randomized 150 mothers with HBV DNA levels greater than > 1000 mEq/mL to lamivudine (100 mg/day daily or placebo, from week 32 of their pregnancy until four weeks postpartum. The newborns received recombinant HBV vaccine with or without HBIg. Within the group of infants in whom the mother received lamivudine plus passive-active immunoprophylaxis (n = 56), the frequency of HBsAg-positive infants was 10 of 56 (18%). In contrast, in the placebo group, in which the infants received passive-active immunization beginning at birth (n = 59) with no maternal antiviral treatment, the incidence of HBsAg-positive infants was 23 of 59 (39%; *P* = .014). The number of infants with detectable HBV DNA levels was 11 of 56 (20%) among lamivudine-treated mothers vs. 27 of 59 (46%) among placebo-treated mothers (*P* = .003). These data demonstrated a significant decrease in the risk for HBV transmission when lamivudine therapy was initiated in the third trimester of pregnancy.

In this study, newborns that were lost to follow-up were considered a failure in the statistical analysis. More newborns in the placebo group (18 of 59; 31%) compared with the lamivudine group (7 of 56; 13%) had missing follow-up data. Taking into account this information, without adjusting for missing data, no statistically significant difference in HBsAg positivity was observed between the two groups of infants (*P* = .368).

The seven antiviral agents approved for the treatment of HBV infection include adefovir dipivoxil (pregnancy category C), interferon alfa-2b (pregnancy category C), pegylated interferon alfa-2a (pregnancy category C), entecavir (pregnancy category C), lamivudine (pregnancy category C), tenofovir (pregnancy class category B), and telbivudine (pregnancy category B). According to the Antiretroviral Pregnancy Registry 2011 interim report, the most of the available data regard treatment during pregnancy currently with focus on lamivudine and tenofovir in the Antiretroviral Pregnancy Registry 2011 Interim Report on antiretroviral use in pregnant women from January 1, 1989, through July 31 2011,[2] when a fetus is exposed to lamivudine during the second or third trimester of pregnancy, there is a 2.8% prevalence of birth defects (178 of /6427).[2] Tenofovir demonstrated similar results, with a 2.1% prevalence of birth defects (15 of /714). 2 These data are similar to the overall risk of for birth defects reported in the general population.[2] Telbivudine has been shown in animal studies to be safe during pregnancy, with no effects on male or female fertility; however, limited human data are available, and those are presented in the review that follows. Clinicians should note that the use of interferon and peginterferon is not considered safe during pregnancy because of the antiproliferative effects of these agents.

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EFFICACY AND SAFETY OF TELBIVUDINE DURING PREGNANCY FOR THE PREVENTION OF HBV TRANSMISSION

Han GR, Cao MK, Zhao W, et al. **A prospective and open-label study for the efficacy and safety of telbivudine in pregnancy for the prevention of perinatal transmission of hepatitis B virus infection.** *J Hepatol.* 2011;55(6): 1215-1221.

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Han and collaborators recently presented data on the efficacy and safety of telbivudine use during late pregnancy in reducing HBV transmission among highly viremic, HBeAg-positive mothers. In this open-label study, a total of 229 Chinese women with HBeAg-positive chronic HBV infection and high viremia (HBV DNA levels > 1.0×10^7 copies/mL) were treated with telbivudine 600 mg/day from 20 to 32 weeks' gestation (n = 135) or served as untreated controls (n = 94). All infants in both treatment arms received 200 IU of HBIg within 12 hours postpartum and 20µg of recombinant HBV vaccine at 0, 1, and 6 months. The results of the study showed that telbivudine treatment was associated with a significant reduction in serum HBV DNA levels and biochemical normalization of elevated alanine aminotransferase levels prior to delivery. Of the 135 telbivudine-treated mothers, 44 (33%) had DNA levels < 500 copies/mL at delivery, compared with none (0%) of the untreated controls. Seven months after delivery, perinatal transmission rates were lower among the infants born to telbivudine-treated mothers who completed follow-up than among the controls (0% vs. 8%; *P* = .002). No serious adverse events were reported among the telbivudine-treated mothers or their infants. The authors concluded that telbivudine appeared to reduce mother-to-child HBV transmission and was well tolerated when administered during pregnancy.

The safety concerns over the effects of antiviral therapy on the developing fetus may be partially mitigated by restricting antiviral therapy to use in the third trimester, as opposed to use throughout the duration of a woman's pregnancy. Recent data on antiviral use in the second trimester yielded no additional transmission benefits among pregnant patients.[1] Other concerns do remain, however, regarding antiviral use in pregnant women. There are reports of lactic acidosis and hepatic steatosis among pregnant patients receiving nucleoside/nucleotide analogues. For this reason, it is important to monitor liver enzymes and serum electrolytes if women are to receive such treatments during pregnancy. Development of rapid and frequent drug-resistant HBV has been well documented with lamivudine, and this is a particularly relevant issue in among patients with high levels of HBV DNA levels. For this reason, lamivudine is not the optimal drug of choice if a mother has an indication for a long-term CHB chronic HBV treatment beyond pregnancy. Acute exacerbations have also been reported after following discontinuation of antiviral therapy after delivery. Withdrawal flares in the general population have been associated with discontinuation of lamivudine and occur in up to 25% of patients.[2] This is in contrast to 62% of patients who developed postpartum flares after receiving amivudine during the last four weeks of pregnancy.[3]

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BREASTFEEDING OF NEWBORNS BY HBV-INFECTED MOTHERS

Shi Z, Yang Y, Wang H, et al. **Breastfeeding of newborns by mothers carrying hepatitis B virus: a meta-analysis and systematic review.** *Arch Pediatr Adolesc Med.* 2011;165(9):837-846.

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Breastfeeding of newborns by HBV-infected mothers has been controversial, as data have shown that HBV is present in breast milk.[1] Given the lack of data demonstrating increased transmission risk, the American College of Obstetricians and Gynecologists now recommends that HBV-infected mothers be allowed to breastfeed their infants.[2]

Shi and associates undertook a meta-analysis of all relevant studies conducted on HBV infection specifically with respect to breastfeeding in the English and Chinese peer-

reviewed literature from 1990 to 2010. In their analysis, the authors included only studies that contained extensive data on intrauterine infection (i.e., infant data collected at the time of birth), appropriate immunoprophylaxis administration, breastfeeding for at least one month, and follow-up through 6 to 12 months of age. The primary outcome of this analysis was the rate of mother-to-child transmission of HBV and anti-HBC production in infants at 6 to 12 months of age. Other secondary analyses included rates of newborn infection at the time of birth and presence of HBV in breast milk and maternal blood.

Ten studies, all conducted in Chinese mothers, were included in the meta-analysis; eight in which HBIg was administered to the newborn and three in which only HBV vaccine was given. The studies included a total of 1624 subjects. No significant difference was reported in mother-to-child transmission of HBV among breastfed babies compared with nonbreastfed babies (odds ratio, 0.86; 95% confidence interval, 0.51 to 1.45), even when vertical transmission risks were taken into account. According to the authors, this meta-analysis provides strong evidence that breastfeeding does not contribute to mother-to-child transmission of HBV in the setting of appropriate immunoprophylaxis.

In current practice, all pregnant women should be screened for HBV in the first trimester. If they test positive for HBsAg, further management should be initiated. At this time, no recommendations have been made to change the mode of delivery, as there is little convincing evidence that Caesarean section reduces a woman's risk for mother-to-child transmission of HBV infection compared with vaginal delivery.[3]

Once delivery occurs, a multidisciplinary effort must be made to initiate HBV vaccination and HBIg administration to the neonate as soon as possible, preferably within the first 12 to 24 hours.[4] As highlighted in the current study, breastfeeding can be initiated; however, the mother should be educated that cracked or bleeding skin or nipples should prompt immediate care and deferral of breastfeeding until healed. The infant should then complete the recommended vaccination schedule, and at 9 to 18 months of age, the infant should be assessed for exposure to HBV and the child's chronic infection status should be determined.

This meta-analysis appears to confirm the current practice of allowing breastfeeding in women chronically infected with HBV who give birth. Future prospective studies are needed to stratify risk factors for mother-to-child transmission of HBV.

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COMPLETE THE POST-TEST

Step 1.
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PHYSICIAN POST-TEST

NURSE POST-TEST