Chronic Hepatitis B Infection and Pregnancy

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It is estimated that 350 to 400 million individuals worldwide are chronically infected with hepatitis B virus (HBV). In regions of high endemicity, many of these are females of reproductive age who are an important source for perinatal transmission. There are a number of issues specific to the women of childbearing age who have chronic HBV infection, including the safety of antiviral therapy during pregnancy and breast-feeding, the changes in the immune system during pregnancy and postpartum that may impact on the natural history of HBV, and the emerging role of antivirals to reduce perinatal transmission of HBV. For women in their reproductive years who require treatment, many of the available antivirals have not been studied in pregnant or breast-feeding women and their use requires the development of a carefully considered strategy, considering the impact of both the disease and treatment on the mother and fetus/infant. The purpose of this article is to (1) review data regarding the mechanisms and timing of perinatal HBV infection; (2) review data on interventions, particularly antiviral therapy, to reduce perinatal transmission beyond the protection afforded by hepatitis B immunoglobulin and vaccination; (3) summarize the immunological changes associated with pregnancy and the potential effect these may have on the natural history of HBV infection; and (4) summarize the information currently available for antiviral therapy available for HBV treatment, focusing specifically on safety data pertaining to reproduction, pregnancy, and breast-feeding.

Target Audience: Obstetricians & Gynecologists and Family Physicians

Learning Objectives: After completing this CME activity physicians should be better able to classify the interventions to reduce mother-to-child transmission of hepatitis B including antivirals, caesarean section, hepatitis B immunoglobulin and hepatitis B vaccine, assess the immunological changes associated with pregnancy and the potential effect this may have on the natural history of HBV infection and apply the information currently available for antiviral therapy licensed for HBV treatment, focusing specifically on safety data in pregnancy and during breastfeeding.
Hepatitis B virus (HBV) is an epidemic of global proportions with severe sequelae. It is estimated 350 to 400 million individuals worldwide are chronically infected.\(^1\) Approximately 600,000 people die each year secondary to the acute or chronic consequences of HBV,\(^1\) and mathematical models have estimated the lifetime risk of death from cirrhosis and hepatocellular carcinoma may be as high as 27% for those with chronic infection.\(^2\) In regions of high endemicity, infection is most commonly acquired through either perinatal or horizontal transmission.\(^3\) Exposure to HBV early in life (either through perinatal or horizontal exposure) is associated with rates of chronic infection in the child of up to 90%, with the risk of chronic infection progressively decreasing with increasing age of exposure.\(^4,5\) Females of reproductive age with chronic HBV infection therefore remain an important source for the ongoing epidemic.

Many women who require treatment for chronic HBV infection are in their reproductive years, and there are a number of issues specific to this population. The number of medical therapies available for HBV has increased during the past 10 years, and now it includes pegylated interferon, lamivudine, entecavir, tenofovir, adefovir, and telbivudine, although many of these have not been studied in pregnant or breast-feeding women. The management of such patients, therefore, requires the development of a carefully considered management strategy, considering the potential impact of both the disease and treatment on the mother as well as on the fetus and infant. Specific issues that need to be considered include the efficacy of therapy, the future reproductive intent of the woman, and safety data of various therapies when used during pregnancy and breast-feeding. There are emerging data suggesting that the addition of antiviral therapy may provide benefit greater than the protection afforded by administration of hepatitis B immunoglobulin (HBIG) and hepatitis B vaccination in reducing perinatal transmission in women who are hepatitis B e antigen (HBeAg) positive with a high viral load.\(^6\) Finally, pregnancy and the postpartum period are associated with unique immunological changes that impact on the natural history of HBV and may result in postpartum hepatitis flares that are unrecognized but may require management.

The purpose of this article is to (1) review data regarding the mechanism and timing of perinatal HBV infection; (2) review data on interventions, particularly antiviral therapy, to reduce transmission; (3) summarize the immunological changes associated with pregnancy and the potential effect these may have on the natural history of HBV infection; and (4) summarize the information currently available on antiviral therapy that is available for HBV treatment, focusing specifically on safety data pertaining to reproduction, pregnancy, and breast-feeding.

**MODE OF HBV TRANSMISSION**

It has been known for many years that mother-to-child transmission of HBV can occur efficiently in the presence of chronic maternal HBV infection, and that transmission rates in children born to HBeAg-positive mothers, in the absence of strategies to interrupt transmission, will result in almost 90% of children becoming chronically infected compared with rates of approximately 30% in children born to HBeAg-negative mothers. The ineffectiveness of a targeted strategy to identify at-risk mothers for screening, as well as the emergence of highly effective methods to interrupt transmission, has resulted in the recommendation of a universal screening strategy in most developed countries.\(^7\)

The potential timing of HBV infection early in life includes in utero transmission, transmission through the process of labor and delivery, and horizontal transmission in childhood. The exact mechanism of each of these modes of transmission and relative contribution in endemic countries is unclear. Studies attempting to investigate in utero transmission have defined this as the neonate demonstrating detectable hepatitis B surface antigen (HBsAg) or detectable HBV DNA on a peripheral venipuncture within 24 hours of delivery.\(^8\) The suggested mechanism is via transplacental spread with 1 case-control study suggesting an association with maternal HBeAg positivity and threatened preterm labor.\(^8\) These investigators also examined 101 placentas and reported a progressive decline in the intensity of staining of HBV DNA from the maternal side to the fetal side of the placenta,\(^8\) a finding that has been confirmed by others.\(^9\) Intrauterine infection in this study was highly associated with the presence of HBV DNA on villous capillary venous cells, the placental cells closest to the fetal circulation. It is, however, not clear whether active HBV replication in placental cells and/or partial placental leakage leading to mixing of fetal and maternal blood is required for transmission. If significant transplacental transmission does occur, the exact timing within pregnancy is unclear, but such occurrence is potentially important as the current interventions of passive and active immunization administered only at delivery will not be effective in preventing transmission via this mechanism and may at least partially explain residual transmission despite such interventions.

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There are very limited data to elucidate the proportion of HBV transmission that occurs through the process of labor and delivery compared with in utero transmission, as the majority of studies define infected infants based on test results performed after the first month of life and do not consistently test the neonate’s peripheral blood for HBsAg and/or HBV DNA at birth. One study evaluated 42 babies at birth for hepatitis B serological markers and HBV DNA and followed them up for 24 months. Four of 16 babies born to HBsAg-positive mothers became chronically HBsAg positive, despite the administration of HBIG and vaccine. Two of these infants were HBsAg-positive and HBV-DNA-positive at birth, suggesting that transplacental transmission may occur in a proportion of cases. This study also demonstrated that in uninfected children, passive maternal transfer of HBeAg can be transiently detected until 4 months of age and that antibody, especially anti-HBc, can persist for longer than a year.

Horizontal transmission (infection acquired in early childhood after delivery) is well recognized, although its relative contribution to childhood infection after delivery is unclear. Identified risk factors include father-to-child contact, sibling contact, and medical procedures such as intramuscular injections. Some studies have attempted to estimate the relative proportion of childhood-acquired chronic hepatitis B infection attributable to horizontal transmission compared with vertical transmission. A study in Japan, at the time of an “at-risk” vaccination strategy, reported that 35% of cases were a result of horizontal transmission. Other studies have attributed a much higher proportion of infections to horizontal transmission, with rates of up to 80% reported from a study across 4 provinces in China conducted before the introduction of a widespread vaccination program. Furthermore, phylogenetic analyses of the HBV isolates obtained from family members of HBsAg-positive children suggest transmission in a vaccinated group was exclusively perinatal, whereas in the unvaccinated group, a horizontal transmission pattern predominated. Given that HBV transmission can be vertical (either in utero or during labor and delivery) or horizontal, a prevention strategy should consider interventions during pregnancy as well as after birth.

**Interventions to Reduce HBV Transmission**

Interventions examined for their potential to reduce HBV transmission include administration of HBIG prenatally to the mother or postnatally to the neonate, cesarean delivery, hepatitis B vaccination to the neonate, and maternal antiviral therapy. The current recommended practice worldwide to reduce transmission of HBV from mother to child is the administration of HBV vaccination and HBIG after delivery; this strategy has been shown to reduce transmission by up to 90%. This approach, however, will not be effective in interrupting in utero transmission. Furthermore, antiviral therapy limited to late pregnancy, as discussed later in the text, will only be effective if transmission occurs predominantly in the third trimester or later.

Two randomized, controlled trials of HBIG administered every 4 weeks from 28 weeks’ gestation until delivery have reported a statistically significant reduction of in utero transmission rates in the intervention group compared with a control group (although 1 study only reported follow-up until 24 hours postpartum). In addition, a recent meta-analysis of both the English and Chinese medical literature has reported an odds ratio in favor of HBIG in reducing HBV intrauterine transmission, defined as a positive HBsAg in the infant at 6 to 9 months of age (odds ratio: 0.22 [0.17, 0.29]). However, this was no longer statistically significant in either the subset including only the HBeAg-positive or HBeAg-negative groups, but did remain statistically significant in the studies where maternal HBeAg status was not known. The possible efficacy of HBIG given after 28 weeks’ gestation in reducing transmission suggests that intratuterine transmission may occur in late pregnancy.

There has also been 1 nonrandomized study examining the role of cesarean delivery in reducing transmission of HBV. Infants received either vaccine alone or vaccine with HBIG (if “high risk,” not further defined) and were followed to 6 months of age. There was no difference in transmission rates between different modes of delivery in infants receiving vaccine alone, but HBV infection rates were lower in those delivered by cesarean delivery in the infants who received HBV vaccine plus HBIG. In a subsequent study, no difference was found in the rate of infants positive for HBsAg at 12 months according to mode of delivery. In contrast, a report pooling together trial data from the English and Chinese medical literature has shown a protective effect with cesarean delivery in preventing HBV transmission. However, there was no reported maternal or infant morbidity, no clear description of randomization procedure, methodological details were not reported, and there was no intention-to-treat analysis or mention of loss to follow-up or study withdrawal. Therefore, drawing conclusions from this should be done with caution. Although interesting and provocative, currently there is insufficient evidence to...
recommend cesarean delivery in this setting, especially given the emerging role of antiviral therapy in late pregnancy.

It has previously been reported that infants born to HBeAg-positive women have reduced rates of efficacy of HBV vaccine and HBIG at delivery, especially in the setting of high-level maternal HBV DNA. This has been further reinforced by a recent study demonstrating that a high maternal HBV DNA viral load (>10^8 copies/mL) was associated with a significantly greater risk of the infant becoming chronically infected with HBV, despite HBIG and HBV, vaccine. In this report, 9% of women with a high viral load transmitted HBV to their offspring compared with none below this threshold.25

These data have spawned an interest in the potential utility of antiviral therapy in late pregnancy to further reduce this rate. This principle has been well established in human immunodeficiency virus (HIV)-infected mothers, where the effect of antiretroviral agents (which include lamivudine) on the reduction of mother-to-child transmission of HIV has been studied extensively and proven to be efficacious.26,27 Lamivudine was the first agent to be studied in relation to prevention of HBV transmission. Lamivudine treatment during the last 4 weeks of pregnancy was demonstrated to prevent perinatal transmission in 3 pregnant women with HBV viral loads >1.2 \times 10^9 \text{ g Eq/mL}.28 A further cohort of 8 HBV-infected pregnant women with high HBV DNA (>10^9 \text{ g Eq/mL}) receiving lamivudine before delivery (range, 6–40 days) reported 1 (12.5%) child remaining HBsAg positive and HBV DNA positive at 12 months of age compared with 28% of historical controls.29 In another cohort, no perinatal transmission of HBV was observed in 12 children (followed to 12 months of age) born to HBeAg-positive pregnant women receiving lamivudine before delivery.30 Most recently, lamivudine treatment for HBV during pregnancy was assessed in a randomized, placebo-controlled study of 114 women conducted in China and the Philippines.6 Although the intention-to-treat analysis of the study suggested a significant reduction in HBV transmission to infants whose mothers received lamivudine (10/56, 18% lamivudine vs. 23/59, 39% placebo; \( P = 0.014 \)), there was a very high loss to follow-up rate in the placebo arm leading to the potential for significant bias. Attempts to adjust for this by sensitivity analyses resulted in a loss of statistical significance leading to criticism of the study. More recently, a systematic review and meta-analysis of both the English and Chinese medical literature of lamivudine in late pregnancy to interrupt in utero transmission has been reported. The results of this review concluded that the incidence of intrauterine transmission in the lamivudine group was 13% to 23.7% lower as measured by HBsAg in newborns. Furthermore, they determined that there was a 1.4% to 2.0% lower mother-to-child transmission rate at 9 to 12 months indicated by HBsAg and HBV DNA.31 Therefore, the issue of efficacy is still unresolved, and it highlights the need for a properly designed, prospective, randomized, controlled trial to address the question of the efficacy of antiviral therapy in the interruption of vertical transmission.

Telbivudine is the only other antiviral that has been studied prospectively in pregnant women, with the outcome of interest being perinatal HBV transmission.32 In a prospective, nonrandomized, open-label study, 190 HBeAg-positive women with HBV DNA viral load >6,000,000 copies/mL were given either telbivudine from 20 to 32 weeks’ gestation or no antiviral. All infants received HBIG and vaccine at delivery. Undetectable viral load was achieved by 30% of women in the telbivudine group compared with none in the untreated arm. At birth, 6.32% of newborns in the telbivudine arm were compared with 30.43% in the control arm, a highly significant difference. HBsAg and HBV DNA results from infants at 28 weeks of age were used to determine perinatal transmission rate. The primary intent-to-treat (missing data were included as infection) analysis at week 28 showed that 2.11% of infants were HBsAg positive or had detectable HBV DNA in the telbivudine arm, compared with 13.04% in the control arm. No congenital deformities or birth defects were seen in infants born to treated or untreated mothers, and no women discontinued medication due to serious adverse events. An ALT flare (2–5 times the upper limit of normal) occurred in 7.45% of women in the telbivudine arm compared with 18.48% in the control arm.32

These recent data on telbivudine introduce the question as to whether these, and other more potent antiviral agents such as tenofovir, may be even more efficacious than lamivudine. To date, none of these have been compared head-to-head in a randomized clinical trial with the primary outcome being perinatal HBV transmission.

Although markers of HBV infection have been found in breast milk, a recent meta-analysis and systematic review has confirmed that provided proper immunoprophylaxis is administered, breastfeeding does not contribute to mother-to-child transmission of HBV.33
Immunological Changes During Pregnancy and HBV

One of the most intriguing, yet poorly studied, issues in modern immunology involves the “paradox of pregnancy,” in which immunologic tolerance to paternally derived fetal antigens is achieved despite, for the most part, an apparently adequate maternal defense against infection. All maternal immune system tolerates fetal antigens by suppressing cell-mediated immunity while retaining normal humoral immunity. These changes are known to occur locally at the maternal–fetal interface but may also affect systemic immune responses to infection. Previous research into the changes in the immune system is extremely heterogeneous, with different reports focusing on different aspects of the immune system, and including different populations of pregnant women of interest. A summary of findings from women with “normal pregnancies” from publications that specify the trimester of the blood sample is mentioned in Table 1.

At a local level, the fetus is exposed to the maternal immune system at the placental and fetal membranes collectively described as the maternal–fetal interface. Despite the prolonged direct exposure of maternal blood to fetal antigens, the immune system does not recognize the fetus as foreign. Several mechanisms underlie this maternal tolerance of fetal tissues. During pregnancy, macrophages at the maternal–fetal interface release predominantly Th2 (subset of helper inducer T lymphocytes)–stimulating cytokines leading to a phenomenon often referred to as the Th1-Th2 shift of pregnancy. This shift is thought to contribute to maternal tolerance of the fetus by suppressing the antifetal cell-mediated immune response. As a consequence, in the uterine decidua, the Th2 cytokine environment favors activation of B lymphocytes, resulting in stimulation of antibody secretion and suppression of cell-mediated immunity.

The innate system uses a variety of pattern recognition receptors, the best described to date are the toll-like receptors (TLR). TLRs are mainly expressed on antigen-presenting cells, such as macrophages, natural killer cells, and dendritic cells in peripheral blood, as well as trophoblasts in the placenta. Stimulation of TLRs leads to signaling which in turn activates antigen-presenting cells to induce direct innate immune effects as well as to establish adaptive immunity via upregulation of costimulatory molecule expression. The role of innate immunity is a rapidly emerging area of immunology and has recently been reported to play a major role in the host response to HBV. The role of innate immune responses, apart from cytokine suppression of TNF, has not been investigated in pregnancy, but are also likely to play a major role.

These variations in immunity during pregnancy have long been known to be associated with clinically significant consequences. Although pregnant women are not severely immunosuppressed in the classic sense, it has been recognized for many years that immunologic changes associated with pregnancy may impact on the clinical manifestations of other infectious diseases, including malaria, toxoplasmosis, measles, influenza, varicella, and listeria. In addition, the clinical manifestations of certain autoimmune diseases may vary during pregnancy and in the postpartum period. As HBV is predominantly an immune-mediated disease, it is unclear whether these changes in immune activity during pregnancy and after delivery impact on the activity of the disease; particularly, whether flares can occur after delivery as has been reported with chronic hepatitis C infection and autoimmune hepatitis.

There are also now emerging data that these immune changes can also impact on the natural history of HBV. Two fatal cases of pregnancy-associated flares of HBV have been reported. There is, however, a paucity of data on the changes in clinical and virological markers of chronic HBV, including transaminases and HBV viral load, during pregnancy and postpartum as well as rates of HBeAg seroconversion in the early postpartum period. One retrospective cohort study of 38 pregnant women with

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TABLE 1

Immunological Changes in Pregnancy

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<tr>
<th>Immune System Change</th>
<th>First Trimester</th>
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* Increase.
* Decrease.
* No significant change.

1Fiddes et al. 36
2Kühnert et al. 37
3Saito et al. 38
4Luppi P. 39
5Hikada et al. 40

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Therapy for HBV in Women of Reproductive Age

Medical therapies now available for treating HBV infection include interferon (standard and pegylated), lamivudine, entecavir, tenofovir, adefovir, and telbivudine. Factors influencing the choice of therapy in women of reproductive age relate to safety in pregnancy, the proposed duration of treatment, antiviral efficacy, and the barrier to antiviral resistance. If a woman is contemplating conception, treatment is often delayed (as long as it is safe to do so) until after the woman has decided she no longer wants to consider having further/any children. Some authorities recommend waiting for a normal menstrual cycle before starting therapy, which is mandated by the woman’s clinical status, opt for interferon-based rather than nucleoside/tide analog therapy in women of childbearing age, given that they are often HBsAg positive and that treatment is for a defined period (48 weeks). This is in the hope that the patient undergoes durable HBeAg seroconversion with clinical remission and ideally HBsAg seroconversion without the need for ongoing long-term nucleoside/tide analog therapy and its attendant potential risk of teratogenicity. This approach highlights the crucial role of an adequate assessment of liver fibrosis, such as liver biopsy or noninvasive methods, to assist in making the decision whether to treat or defer therapy.

The safety of oral antiviral agents in pregnancy has therefore become a critical issue in this patient population with decisions based predominantly on animal data and limited human experience as pregnant women are specifically excluded from the majority of clinical trials. The safety of drugs in pregnancy is stratified by the Food and Drug Administration into a classification system on the basis of experience of human exposure and the potential to cause harm to the fetus from animal studies. The main nucleoside/tide analogues recommended for first-line HBV therapy in treatment-naive patients are entecavir and tenofovir because of their high barrier to resistance and antiviral potency. Of the drugs used in the treatment of chronic HBV infection, telbivudine and tenofovir have been given a lower-risk category B Food and Drug Administration classification in pregnancy.

The other major source of information on teratogenicity is derived from the Antiretroviral Pregnancy Registry established in 1989 to evaluate teratogenicity of HIV agents but which has more recently (from 2003) also included antivirals with activity against HBV. The registry is voluntary and collects information on congenital anomalies in offspring born to women exposed to HIV and HBV antiviral agents. It then compares the rate of congenital anomalies with the background rates from sentinel counties in Atlanta. Because of their dual activity for HIV and HBV, and hence more extensive experience in the HIV setting, lamivudine and tenofovir have had the most documented exposures in the registry. Overall, teratogenicity rates have been shown to be equivalent to the background rate of congenital anomalies in the general population. These resources address issues of teratogenicity but do not address the issue of toxicity in exposed infants either during the third trimester or during breast-feeding when teratogenicity is no longer relevant but toxicity may occur. There is a paucity of safety data on breast-feeding and antiviral therapy. This highlights the need for an additional registry to assess the impact of such exposures in children postpartum.

The major issue with lamivudine and telbivudine with prolonged use has been the unacceptable rate of resistance. Whether this becomes a significant problem with short exposures such as those proposed for the prevention of perinatal HBV transmission remains to be seen. Other agents such as tenofovir, with lower reported development of resistance and substantial safety data in pregnancy, albeit from HIV-infected women, have potential benefits in this situation.
CONCLUSION

Many women with chronic HBV who are being considered for treatment are of reproductive age; thus, consideration of their reproductive intention balanced with need for treatment to reduce progressive liver fibrosis is an important aspect of clinical management. Factors to consider include age, extent of existing liver fibrosis, and safety and efficacy data of available licensed anti-HBV medications. Although none of these agents are recommended in pregnancy, there is increasing safety and efficacy data emerging. The implications of this are (1) some women should no longer delay treatment if it is clinically warranted, even if they are trying to conceive; (2) there is a need to conclusively determine whether there is an additional benefit in preventing mother-to-child transmission of HBV with anti-HBV medications, especially using newer, more potent agents; and (3) immune-mediated postpartum HBV flares may offer the optimal time to treat and maximize rates of HBeAg seroconversion, given the unique immunological changes that occur at this time. With such a high burden of disease among women of reproductive age and ongoing perinatal transmission occurring despite widespread use of HBIG and HBV vaccine, further research of this population is urgently needed.

REFERENCES

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