Hepatitis B Virus Infection during Pregnancy: Transmission and Prevention

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ABSTRACT

Hepatitis B virus (HBV) infection is a global public health problem. In endemic areas, HBV infection occurs mainly during infancy and early childhood, with mother to child transmission (MTCT) accounting for approximately half of the transmission routes of chronic HBV infections. Prevention of MTCT is an essential step in reducing the global burden of chronic HBV. Natal transmission accounts for most of MTCT, and providing immunoprophylaxis to newborns is an excellent way to block natal transmission. Prenatal transmission is responsible for the minority of MTCT not preventable by immunoprophylaxis. Because of the correlation between prenatal transmission and the level of maternal viremia, some authors find it sound to offer lamivudine in women who have a high viral load (more than 8 to 9 log 10 copies/mL). In addition to considerations regarding the transmission of HBV to the child, the combination of HBV infection and pregnancy raises several unique management issues. Chronic HBV infection during pregnancy is usually mild but may flare after delivery or with discontinuing therapy. Management of chronic HBV infection in pregnancy is mostly supportive with antiviral medications indicated in a small subset of HBV infected women with rapidly progressive chronic liver disease.

KEYWORDS
Hepatitis B; Pregnancy; Transmission; Prevention

INTRODUCTION

Hepatitis B virus (HBV) infection is a global public health problem. The WHO estimates that more than 2 billion people have been infected with HBV virus at some point in their lives and 350 million people across the world continue to carry chronic HBV infection, of whom almost one million die annually from HBV-related liver disease.[1] HBV is considered to be the cause of 60% of cases of primary liver cancer in the world and the most common carcinogen after cigarette smoking.[2] Although the true prevalence of hepatocellular carcinoma (HCC) in Iran is unknown, it is not an uncommon malignancy; 80% of HCC cases in Iran are positive for at least one of the markers of HBV, and this virus appears to be the most common cause of HCC in Iran.[3, 4]

The prevalence of HBV infection varies worldwide with approximately half the world's population living in regions where HBV infection is endemic, including most of Asia and the Pacific Islands, Africa and the Middle East.[5] The prevalence of HBV

infection in Iran varies between different cities; in a recent population based study in Iran, the rate of HBcAb and HBsAg was found to be 16.4% and 2.6%, respectively which makes Iran an intermediate prevalence country for HBV infection. The wide variation in the global distribution of chronic HBV infection is largely related to differences in the age at infection, which is inversely related to the risk of chronicity. In endemic regions, HBV infection is acquired predominantly during the perinatal period or in early childhood.[6] Chronic infection is much more likely to develop in patients infected as infants (90%) and young children (30%).[7] Although rates of new infection and acute disease are highest among adults, the rate of progression from acute to chronic HBV infection is less than 5% for adult acquired infection.[8]

The risk of maternal-infant transmission is related to the HBV replicative status of the mother which correlates with the presence of HBeAg as 90% of HBeAg-positive mothers transmit HBV infection to their offspring compared to only 10%–20% of HBeAg-negative mothers.[9] The high frequency of perinatal transmission in endemic areas is probably related to the high prevalence of positive HBeAg in women of reproductive age in these countries. Studies have shown that the rate of HBeAg seroconversion during the first 20 years of life is relatively slow, leaving many women of childbearing age who have contracted HBV infection in their early childhood still highly infectious to their infants.[10]

The importance of perinatal transmission becomes paramount, because follow-up data on persons infected as infants or young children demonstrate that about 25% of persons who have chronic infection die prematurely from cirrhosis and liver cancer; the majority of whom are asymptomatic until onset of end-stage liver disease. At the same time, individuals who have chronic infection serve as the major reservoir for continued HBV transmission.[11]

In this article, we review the most important routes of transmission in endemic areas for HBV infection and the strategies to prevent vertical transmission.

Mother to child transmission (MTCT)

The transmission of infections from mother to offspring is traditionally known as perinatal infection. By definition, perinatal period begins from 28 weeks of gestation and ends at 28 days after delivery. Therefore, the term "perinatal transmission" does not actually include infections that occur before or after this time period and thus can be replaced by the term "mother to child transmission (MTCT)" which takes account of all HBV infections contracted before birth, during birth and in early childhood; the importance of which as a group is their remarkably greater risk of chronicity compared to infections acquired later in life.[12]

Theoretically, there are three possible routes for transmission of HBV from an infected mother to her infant:[13]

1. transplacental transmission of HBV in utero
2. natal transmission during delivery
3. postnatal transmission during care or through breast milk

For a newborn infant whose mother is positive for both HBsAg and HBeAg, in the absence of post-exposure immunoprophylaxis, the risk for chronic HBV infection is 70%–90% by age 6 months.[9] HBV vaccination can prevent 70%-95% of HBV infections in infants born to HBeAg and HBsAg-positive mothers.[14] In most post-exposure prophylaxis studies, HBV vaccine has been administered to infants within 12-24 hours of their birth. The efficacy of vaccine in preventing MTCT declines by time after birth.[15] Therefore it has been postulated and widely accepted that most MTCT occur at or near the time of birth (natal transmission).

Pre-natal transmission

Despite the relatively excellent efficacy of high titer HBIG and HBV vaccination as post-exposure prophylaxis (PEP) in newborns, in 3% to 9% of children born to mothers with positive HBV serum markers, this strategy fails to block MTCT of the virus.[16, 17] The rate of PEP failure is 3% in general and 9% from mothers with very high levels of HBV-DNA.[17]

The pre-natal (intrauterine) route of HBV transmission is currently considered the chief culprit behind this failure. The exact mechanism for prenatal transmission of HBV is not fully elucidated yet, however various possibilities are hypothesized including:

1. A breach in the placental barrier:
   Transplacental leakage of HBeAg-positive maternal blood, which is induced by uterine contractions during pregnancy and the disruption of placental barriers (such as threatened preterm labor or spontaneous abortion), is one of the most likely routes to cause HBV intrauterine infection.[18]
   It has been shown that amniocentesis inoculates the intrauterine cavity with maternal blood because the needle traverses the abdominal and uterine wall. However, HBV transmission during amniocentesis appears to be rare, particularly in mothers who are HBeAg-negative and when the procedure is done using a 22-gauge needle under continuous guidance.[19]
2. Placental infection and trans-placental transmission of HBV:
   Placental infection in a fetus with intrauterine HBV infection can either be the route for transmission of HBV from the mother to the fetus or secondary to fetal infection by another route. To distinguish between these two possibilities, researchers have measured the gradient of placental infection between the maternal side and the fetal side of the placenta and concluded that in the majority of cases, transplacental infection is the mechanism for HBV intrauterine infection.[16, 20]
3. Studies have also demonstrated that HBV-DNA exists in oocytes of infected females and sperms of HBV-infected males. Therefore, it is possible for the fetus to become infected with HBV at conception.[20]
4. Another possibility is the intrauterine transmission of HBV to the fetus, not from maternal blood but ascending from vaginal secretions of the mother that contain the virus.[20]

Natal transmission

Transmission of HBV to the infant at the time of birth is believed to be a result of exposure to maternal cervical secretions and maternal blood that contain the virus.[21]

There is still some controversies regarding the effect of delivery mode on MTCT; in current obstetrical guidelines, the mother's HBsAg positivity does not affect the planned mode of delivery irrespective of her HBeAg status or level of viremia. Some articles recommend cesarean section in case of high maternal HBV-DNA levels,[22] whereas others believe that mode of delivery does not influence the rate of HBV transmission provided that all infants receive HBIG and HBV vaccine at the recommended schedule.[23] A recent systematic review in 2008 on four randomized controlled trials (RCTS) involving 789 people concluded that cesarean section before labor or before ruptured membranes (elective cesarean section or ECS) appears to be effective in preventing MTCT of HBV. However, the authors point out that the conclusions of this review must be considered with great caution due to high risk of bias in each included study (graded C).[24] RCTS of higher quality are required for assessing the effects of ECS in comparison to vaginal delivery for preventing MTCT of HBV.

Postnatal transmission

Although HBV-DNA is present in the breast milk of HBV infected mothers, feeding their infants with this milk poses no additional risk for the transmission of HBV provided that appropriate immunoprophylaxis is commenced at birth and continued as scheduled. There is no need to delay breastfeeding until the child has received all doses of HBV vaccine.[25]

Breastfeeding does not have a negative influence on the immune response to the HBV vaccine and does not increase its failure rate.[26] As a general rule, it is recommended to explain to mothers that they should take good care of their nipples while breast-feeding, ensuring proper latch-on and allowing the nipples to dry before covering to avoid cracking or bleeding, having in mind that HBV is commonly passed by blood-to-blood routes.[27]

Prevention of MTCT

In endemic areas, HBV infection occurs mainly during infancy and early childhood, with MTCT accounting for approximately half of the transmission route of chronic HBV infections.[28] Prevention of MTCT is an essential step in reducing the global burden of chronic HBV.[21]

As discussed before, natal transmission accounts for most of MTCT and providing immunoprophylaxis to newborns is an excellent way to block natal transmission. However, prenatal transmission might be responsible for the minority of MTCT.

Prevention of natal transmission

Immunoprophylaxis provided to newborns clearly reduces the incidence of perinatal HBV transmission. Vaccination of neonates of HBsAg-positive mothers is the most important and cost-effective step toward the eradication of chronic HBV infection.[29] A Cochrane systematic review in 2006 has shown that the relative risk of neonatal HBV infection in those who receive HBV vaccine alone, compared with those who receive placebo or no intervention is 0.28, the addition of hepatitis B immune globulin (HBIG) to this regimen further reduces the relative risk to 0.08 when compared with placebo/no intervention.[14] These data indicate that vaccination alone is insufficient to prevent transmission of HBV infection from HBeAg-positive mothers to their infants. Vaccination alone should only be considered in countries where HBIG is not available, in patients that cannot afford the cost of HBIG or in certain remote areas where a laboratory is not accessible for implementation of maternal HBsAg testing.

The standard immunoprophylaxis regimen consists of both passive and active immunizations. HBV vaccine and HBIG are given at the same time at two different injection sites within 12 hours of delivery. The infants then receive two additional doses of HBV vaccine at ages 1-2 months and 6-8 months.[15, 30, 31]

As noted before, even with the prompt administration of this standard immunoprophylaxis regimen, HBV infections in newborns still occur in some infants.

Immunoprophylaxis is not 100% successful in blocking natal transmission either and one putative mechanism of such failure is believed to be mutations in the S gene of HBV that cause conformational changes in the α determinant of HBsAg (the major target for neutralizing antibodies against HBV). Although to date, the negative effect of such mutations on the success rate of immunoprophylaxis programs has not been proven, concern has been expressed that these variants might replicate in the presence of vaccine-induced anti-HBs or anti-HBs contained in HBIG. It has been proposed that enhanced surveillance to detect the emergence of these variants will be necessary for monitoring the effectiveness of current vaccination strategies.[21]

In Iran, all pregnant women are supposed to be tested for HBsAg and neonates born to HBsAg-positive women should receive HBIG and vaccine within 12 hours of birth. All infants, regardless of maternal HBsAg status, should receive HBV vaccine in the first months of life. In Taiwan, great success has been achieved in decreasing HBV carrier rates with mass immunization. After 20 years of a vaccination program in Taiwan, the HBV carrier rate among children younger than 15 years of age has decreased from 9.8% at the start of the program to 0.5% in 2004.[32] In a WHO report in 2007, 171 countries had introduced HBV vaccine into their national immunization program. The estimated global third dose HBV vaccine coverage for infants, however, was only 60% in 2006. This shows that the vaccination rate in most endemic countries is still quite low and there is still a long way from the goal of full implementation of national vaccination programs as recommended by the WHO.[33]

The HBV mass vaccination program in Iran was started in infants in two provinces (Zanjan and Semnan) in 1989, and in 1993 the vaccination was included in the Expanded Program on Immunization (EPI) countrywide. After 13 years of implementation, the coverage has reached an appropriate level from 62% in 1993 to 94% in 2005.[34] Adibi et al.[35] have shown that conducting a universal premarital HBV screening program would be highly acceptable in Iran.

Prevention of prenatal transmission

Transplacental (intrauterine) transmission is presumed to cause the minority of infections not prevented by prompt immunization. Risk factors for transplacental transmission of HBV include:

1. Maternal HBsAg titer:
   Some studies have shown a positive correlation between maternal HBsAg titers and the risk of intrauterine transmission of HBV.[36]
2. Maternal HBeAg positivity:
   HBeAg is a small secretory protein produced by HBV. It can cross the placental barrier from mother to infant. Transplacental HBeAg from the HBeAg-positive mother renders the neonate's T helper cells unresponsive to HBeAg and HBcAg (immune tolerance). This immune tolerance state persists for years to decades after neonatal infection.[37] On the other hand, mother to infant transmission of HBV from HBeAg-negative, HBsAg-positive mothers, is the most important route of transmission for acute or fulminant hepatitis in infancy (immune clearance).[38] This may be one explanation for the fact that 90% of the infants of HBeAg-positive carrier mothers became chronic carriers, while only approximately <5% of the infants of HBeAg-negative HBsAg carrier mothers become chronic carriers.[39]
3. Maternal HBV-DNA levels:
   The risk of maternal-infant transmission is related to the HBV replicative status of the mother. Both maternal HBeAg status and maternal serum HBV-DNA are reliable markers for viral replication and the latter correlates better with the risk of transmission. Vertical transmission of HBV occurs despite postnatal active and passive immunization in 9-39% of infants of highly viremic mothers (≥8 log copies/mL) and the risk correlates well with maternal serum HBV-DNA levels.[17, 40, 41]
4. HBV genotype:
   Eight genotypes of HBV have been defined (forms A–H). Different genotypes are distributed in different geographical areas. For example, genotypes B and C are prevalent in Asia, while genotypes A and D are more common in Europe, the Middle East and India. The prevalence of different genotypes among pregnant women reflects their distribution in the general population in that particular region. Genotype can be a factor

associated with viral load and frequency of vertical transmission. For example, despite a similarly high prevalence of HBV chronic carriers, the rate of MTCT in East Asia is significantly higher than MTCT in sub-Saharan Africa. This difference can be largely attributed to the different natural histories of HBV infections with different genotypes. In East Asia where genotypes B and C prevail, most infected women of gestational age carry HBeAg and high viral loads. In contrast, in sub-Saharan Africa, whether infected with HBV genotype A1 or E, seroconversion to anti-HBe occurs before age 15–16 years, with the consequence that most women of gestational age carry anti-HBe. As noted before, the risk of MTCT is directly related to the maternal HBV replicative status.[12]

Multiple studies have shown genotype D as the only HBV genotype detectable in various clinical forms of HBV in different Iranian populations.[42-48] Some studies comparing the natural course in genotype A and genotype D HBV infection have shown that seroconversion to anti-HBe in genotype D infections is similar to that of genotype A infections, but genotype D infection is associated with a lower rate of sustained remission and HBsAg clearance, and a more severe disease compared to genotype A.[49-51] Other similar studies have shown higher rates of HBeAg positivity in genotype A when compared with genotype D.[52, 53] In a study of 413 patients from Japan that compared genotypes D and C, Duong et al.[54] showed that HBeAg/anti-HBe ratio was significantly lower in genotype D as compared to genotype C.. A study on 109 Iranian patients with a median age of 37 years reported 26.4% of them as HBeAg-positive.[45]

5. Specific polymorphisms in some genes encoding for cytokines (including interferon-γ and tumor necrosis factor-α and IL-10) and human leukocyte antigen (HLA) class II molecules have been associated with increased or decreased susceptibility of the infants to intrauterine HBV infection.[55-57]

A study in adult Iranian patients have shown that HLA-A 13 is closely related with protection against persisting HBV in an Iranian population .These findings emphasized that the host HLA polymorphism is an important factor in determining the outcome of HBV infection.[58] No such study on Iranian infants has been performed to date.

Because of the clear correlation between the risk of intrauterine transmission of HBV with the level of maternal viremia, a growing number of trials have investigated the role of adding additional antiviral therapy with a nucleoside analogue late in pregnancy to standard immunization and prophylaxis to decrease maternal viral load and MTCT. The oral nucleoside analogs indicated for the management of HBV infection are all listed as either a category B or a category C (Table 1) agent by the US Food and Drug Administration (FDA). Lamivudine, adefovir and entecavir are designated category C drugs; telbivudine and tenofovir are category B drugs.

Table 1: Pregnancy category of US Food and Drug Administration-approved treatments for chronic hepatitis B virus.

Drugs	Pregnancy category
IFN-a	C
Peg-IFN-a	C
Adefovir	C
Entecavir	C
Lamivudine	C
Telbivudine	B
Tenofovir	B

Category A drugs: controlled studies in women fail to demonstrate a risk to the fetus.
Category B drugs: no teratogenic/embryogenic risk in animal studies and no controlled human studies available or risk in animal studies, but controlled human studies refute these.
Category C drugs: teratogenic/embryocidal effects in animals, and no controlled studies in humans.
Category D drugs: positive evidence of human fetal risk, but benefits from use in pregnant women may be acceptable despite the risk.

There is a long history of use of lamivudine during pregnancy, both for women with HIV infection and for those with chronic HBV. Studies have indicated that the rate of birth

defects among women exposed to lamivudine is similar to that in the general population.[59] Data on tenofovir exposure in pregnancy has also found no overall increase in congenital anomalies.[60] However, defects in bone mineral density have been observed in HIV infected individuals under long term treatment with tenofovir. Therefore, there is concern about the effect of tenofovir on fetal bone maturation. There has been only limited use of adefovir, entecavir or telbivudine during pregnancy.

Initial trials involving small numbers of subjects have suggested a significant reduction of vertical transmission compared to historical controls when mothers were treated with 4- 12 weeks of lamivudine in the third trimester.[61, 62] Results of a double-blinded RCT in which mothers were randomized to either lamivudine 100 mg or placebo from week 32 of gestation to week 4 postpartum suggest that lamivudine reduced HBV transmission from highly viremic mothers to their infants who received passive/active immunization.[63] However, there was a high dropout rate, particularly among infants of mothers who received placebo. Sensitivity analysis with no adjustments for missing data revealed a substantially lower rate of infection in both groups and a lack of a statistically significant difference between the lamivudine and placebo groups.[10] Also, not all the mentioned RCTs used the same end points. The important end point, which is the presence of HBsAg 9 to 12 months after birth, was included in five studies. Only one of the five studies showed a significant benefit from lamivudine prophylaxis.

A meta-analysis of ten studies concluded that the addition of lamivudine therapy in late pregnancy to the standard HBV vaccination and HBIG prophylaxis significantly reduced MTCT.[64]

Considering the above points, lamivudine prophylaxis is still a controversial issue; however, it might be used in a subset of pregnant women with very high levels of HBV-DNA (i.e., HBV-DNA >8-9 log 10 copies/ml). Another approach to the prevention of intrauterine HBV transmission is provision of HBIG during pregnancy. Several reports have documented the results of this intervention, with some studies reporting a beneficial effect of HBIG during pregnancy,[40, 65, 66] while in others no obvious effect was noted.[67] However, these studies are quite heterogeneous, using different doses and routes of HBIG administration, and utilizing different outcomes to determine neonatal infection. Theoretically, administration of HBIG is unlikely to have a major impact in preventing maternal-infant transmission of HBV, because of the high concentration of HBsAg in the maternal serum.[10]

Recommendation to decrease MTCT

- HBsAg screening:
  All pregnant women (including those previously tested or vaccinated) should be tested routinely for HBsAg during an early prenatal visit (preferably in the first trimester) in each pregnancy. Women who were not screened prenatally, those who engage in behaviors that put them at high risk for infection and those with clinical hepatitis should be tested at the time of admission to the hospital for delivery.[68]
- Immunization of infants born to HBsAg-positive mothers:
  All infants born to HBsAg-positive women should receive single-antigen HBV vaccine and HBIG (0.5 mL/kg) within 12 hours of birth, administrated at different injection sites. The vaccine series should be completed according to a recommended schedule. The final dose in the vaccine series should not be administrated before age 24 weeks (164 days). For preterm infants weighing less than 2000 g, the initial vaccine dose (birth dose) should not be counted as part of the vaccine series because of the potentially reduced immunogenicity of

HBV vaccine in these infants; three additional doses of vaccine (for a total of four doses) should be administrated beginning when the infant reaches the age of 1 month. Infants of HBsAg-positive mothers may be breastfed beginning immediately after birth. Post-vaccination testing for anti-HBs and HBsAg should be performed after completion of the vaccine series, at the age of 9-18 months. Testing should not be performed before the age of 9 months to avoid detection of anti-HBs from HBIG administrated during infancy and to maximize the likelihood of detecting late HBV infection. HBsAg-negative infants with anti-HBs levels of 10 mIU/mL or more are protected and need no further medical management. HBsAg-negative infants with anti-HBs levels less than 10 mIU/mL should be revaccinated with a second three dose series and retested 1-2 months after the final dose of vaccine. Infants who are HBsAg-positive should receive appropriate follow up and treatment.[68]

- Immunization of infants born to women with unknown HBsAg status:
  Women admitted for delivery without documentation of HBsAg test results should have blood drawn and tested as soon as possible after admission. While test results are pending, all infants born to women without documentation of HBsAg test results should receive the first dose of single-antigen HBV vaccine (without HBIG) 12 hours or less after birth. If the mother is determined to be HBsAg-positive, her infant should receive HBIG as soon as possible but no later than the age of 7 days, and the vaccine series should be completed according to a recommended schedule for infants born to HBsAg-positive mothers. If the mother is determined to be HBsAg negative, the vaccine series should be completed according to a recommended schedule for infants born to HBsAg-negative mothers. If the mother has never been tested to determine her HBsAg status, the vaccine series should be completed according to a recommended schedule for infants born to HBsAg-positive mothers. Administration of HBIG is not necessary for these infants. Because of the potentially decreased immunogenicity of vaccine in preterm infants weighing less than 2000 g, these infants should receive both single-antigen HBV vaccine and HBIG (0.5 mL) if the mother's HBsAg status cannot be determined within 12 hours or less after birth. The birth dose of vaccine should not be counted as part of the three doses required to complete the vaccine series; three additional doses of vaccine (for a total of four doses) should be administrated according to a recommended schedule on the basis of the mother's HBsAg test result.[68]
- At this point, there is no consensus regarding using either HBIG, a nucleoside analogue, or ECS in pregnant women to prevent MTCT. One proposed algorithm includes consideration of both the level of maternal viremia and the history of a previous child becoming infected with HBV perinatally for decision making.[69] Some authors find it sound to offer lamivudine in women who have a high viral load (more than 8 to 9 log 10 copies /mL). Treatment should be started preferably 6 to 8 weeks before delivery and be continued until 4 to 8 weeks after delivery.[10]

Management of chronic HBV infection in pregnancy

Women with chronic HBV generally do well during pregnancy, with reactivation of the virus and exacerbation of the disease during or after gestation uncommon. Management of chronic HBV infection during pregnancy is mostly supportive. Patients need to be monitored periodically with liver function tests during preg-

nancy. A small subset of HBV infected women with rapidly progressive chronic liver disease may be treated with antiviral medications. In women who are expected to receive long-term treatment, tenofovir is a better choice than lamivudine because of the lower risk of resistance associated with its use.[70]

A proportion of women have hepatitis flares with or without HBeAg seroconversion within the first months after delivery.[71] Although this is usually well tolerated, cases of exacerbation of hepatitis and even fulminant hepatic failure have been described in the peripartum period.[72, 73] Exacerbation of hepatitis is not prevented by administration of lamivudine in the third trimester.[72]

Discontinuing therapy in women who become pregnant while receiving antivirals can also cause hepatitis flares. In these cases, the teratogenicity of the drug should be weighed against the risk of hepatitis flare in each individual case. In women with mild hepatitis with a low risk of serious flare or disease progression, stopping therapy, monitoring serum HBV-DNA concentration and ALT activity throughout the pregnancy and restarting therapy during the post-partum phase is a reasonable option. In women with more severe diseases and higher risk of hepatitis flare, it might be better to continue antiviral therapy during pregnancy (if antivirals other than lamivudine or tenofovir are used, women should switch to lamivudine or tenofovir for the duration of the pregnancy, or permanently).[12, 21]

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