Hepatitis-B in Pregnant Woman and Their Neonatal Outcomes: Do vaccines effectively reduce Transmission?

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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

HBV is effectively transmitted via percutaneous or mucosal exposure to infectious blood or bodily fluids that contain blood. In regions of high endemicity, perinatal transmission from an infected mother to her newborn child remains an important mode of HBV infection, although there is also a substantial contribution from early horizontal transmission between infected family members or other individuals.

For an infant whose mother is chronically infected and has serologic evidence of active HBV replication based on detection of hepatitis B e antigen (HBeAg), the risk for chronic HBV infection is high and ranges from 70% to 90% by the age of 6 months in the absence of passive immunoprophylaxis with hepatitis B immunoglobulin (HBIg) and hepatitis B vaccination.

Children born to HBeAg-negative mothers have a lower risk of infection that ranges from 10% to 40%, although most of those who do get infected will also develop chronic infection. Standard passive-active immunoprophylaxis with HBIg and hepatitis B vaccination administered immediately after birth to infants of HBsAg-positive mothers significantly reduces the risk of HBV transmission. However, despite these measures, 5% to 10% of infants born to HBeAg-positive mothers subsequently become HBsAg-positive. This infection rate may be related to high levels of maternal viremia, intrauterine infection, or HBV mutation of the surface protein

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.

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

1. trans placental 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. HBV vaccination can prevent 70%-95% of HBV infections in infants born to HBeAg and HBsAg-positive mothers. 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. 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. The rate of PEP failure is 3% in general and 9% from mothers with very high levels of HBV-DNA.

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.

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.

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, trans placental infection is the mechanism for HBV intrauterine infection.

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.

4. Another possibility is the intrauterine trans-mission of HBV to the fetus, not from maternal blood but ascending from vaginal secretions of the mother that contain the virus.

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.

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, 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. 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). 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.

Breastfeeding does not have a negative influence on the immune response to the HBV vaccine and does not increase its failure rate. 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.

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.

• 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.

• 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.

• 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.

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 pregnancy. 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.

A proportion of women have hepatitis flares with or without HBeAg seroconversion within the first months after delivery. 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).

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