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Review Article

Management and Elimination of mother-to-child transmission of hepatitis B virus: A therapeutical Approach

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Abstract

A major worldwide health issue is the persistent transmission of the chronic form of the hepatitis B virus (HBV) from mothers to their unborn children (MTCT) during the perinatal period. In endemic areas, HBV infection occurs mainly during infancy and early childhood, with MTCT accounting for approximately half of the transmission routes of chronic HBV infections. Prevention of MTCT is an important step in reducing the global burden of chronic HBV. In addition to such considerations regarding the transmission of HBV to the child, the combination of HBV infection and pregnancy raises several unique management issues. Up to 9% of newborns still acquire HBV infection, especially from mothers who have the hepatitis B e antigen (HBeAg), despite routine passive-active immunoprophylaxis with hepatitis B immunoglobulin (HBIG) and the hepatitis B vaccine. The failure of passive-active immunoprophylaxis in newborns, the impact and requirement of routine hepatitis B immunoglobulin (HBIG) injections to mothers, the safety of antiviral prophylaxis, and the safety of nursing are some of the complications associated with managing HBV infection throughout pregnancy. Chronic HBV infection during pregnancy is usually but may flare after delivery. These unresolved issues are highlighted in this review and we aim to an optimal approach to the management of preventing MTCT of HBV infection.

Keywords: Hepatitis B, perinatal period transmission, immunoprophylaxis, breastfeeding, viremia.

Introduction

Hepatitis is an inflammation liver. Viral hepatitis is the most common type of hepatitis. It is caused by one of several hepatitis viruses A, B, C, D, E. Hepatitis B is potentially life-threatening liver infection caused by the hepatitis B virus (HBV). It can cause chronic infection and put people at high risk of death from cirrhosis and liver cancer. Chronic hepatitis B virus infection is an important global health problem. According to World Health Organization estimated that globally, in 2015, 300 million people were suffering with chronic HBV[1, 2]. Most of them contract their infections during pregnancy or in early childhood, particularly in locations with high endemicity.[3] An estimation of 1.5 million new infections are seen annually. According to previous studies, 90% of newborns have a chance to become chronic carriers after infection with HBV and in children less than 3-year-old the chance is up to 50%, but in adults the chance is up to 5%. For this reason, vertical transmission, also called mother to child transmission (MTCT), during pregnancy or perinatal periods, has been recognized as the most important phase for the prevention of chronic HBV infection.[4]

Strategies for preventing HBV infection during pregnancy include vaccination, combined with hepatitis B immunoglobulin (HBIG) administration, and nucleoside/nucleotide analogs. These methods have reduced carrier rate in pregnant women with high HBV DNA, but eradicating MTCT remains a challenge due to 10% of individuals affected by intrauterine infection and immunoprophylaxis failure.[5]

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 compared to only 10%-20% of HBeAg -negative mothers. 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[6]. There are several odd reasons why managing HBV infection during pregnancy is challenging such as: (1) passive-active immunoprophylaxis failure in several newborns, (2) HBIG injection- its effects and necessity in mothers, (3) safety of utilizing nucleoside/nucleotide analogues for antiviral prevention, (4) different delivery ways and its benefits, (5) safety of breastfeeding[7].

Mother to Child Transmission (MTCT)

The transmission of infections from mother to offspring is traditionally known as perinatal infection. For a newborn infant whose mother is positive with HBeAg, in the absence of immunoprophylaxis, the risk of chronic HBV infection is 70%-90% by the age of 6 months. Perinatal transmission of HBV

results in a high frequency of chronic infection, up to 90% in infants born to HBeAg-positive women[8]. Transplacental transmission of HBV include maternal HBeAg positivity and HBV DNA level[9]. The three possible ways an infant get infected to HBV from an infected are:

1. Transplacental transmission of HBV in utero
2. Natal transmission during delivery
3. Postnatal transmission through breast milk

Pre-natal transmission

The pre-natal (intrauterine) route of HBV transmission is currently considered as an important culprit behind this post-exposure prophylaxis (PEP) which failed to block the MTCT of the virus[10].

Exact mechanism for prenatal transmission of HBV is unknown yet, however various possibilities are hypothesized including:

1. A Breach in the placental barrier: There will be a transplacental leakage of HBeAg- positive maternal blood flow, which will cause disruption of placental barrier due to induced uterine contractions during pregnancy, which is one of the most common ways to cause HBV intrauterine infection.
2. Placental infection and trans-placental transmission of HBV: Placental infection in a fetus with intrauterine HBV infection can be of 2 types, i.e., route for transmission of HBV from mother to fetus or secondary fetal infections by other routes. To differentiate these 2 outcomes, researchers have measured the gradient of placental infection between the mother side and fetal side of placenta and concluded that in majority of the cases, transplacental infection is the mechanism for HBV intrauterine infection[11].
3. From recent studies, researchers have revealed that HBV-DNA in the eggs of infected females and also in the sperms of HBV infected males. Therefore, it is possible for the fetus to get effected by the HBV at conception.
4. Other possibility is the intrauterine trans-mission of HBV to fetus, not from the maternal blood but the vaginal secretion of the mother which leads to this type of transmission[12].

Natal transmission:

Natal transmission usually takes place at the time of birth where the transmission of HBV takes place and passes to the infant and it is believed to be a result of exposure to maternal blood and also maternal cervical secretion which contain the virus. It is observed that there are still some controversies which are affecting the mode of delivery on MTCT. Some researchers have recommended cesarean section in case of high maternal HBV-DNA levels, whereas others believe that mode of delivery does not influence the rate of HBV as all the infants will be provided with HBIG and HBV vaccine at the recommended schedule[13].

Postnatal transmission

This type of transmission takes place when feeding the infants with Breastmilk. But, feeding their infants with this milk affects no additional risk is transmitted (HBV) provided that appropriate immunoprophylaxis is commenced at birth and continued as scheduled. There is no need of delaying the breastmilk to the infant until the child is received with all the doses of HBV vaccine[14].

Mechanism of MTCT of HBV

The mechanism of MTCT is important for the management of chronic HBV infection. Perinatal transmission is the main mode of HBV transmission. There are three possible routes for transmission of HBV: transplacental transmission in utero (intrauterine transmission), natal transmission during delivery (intrapartum transmission) and postnatal transmission through breastmilk (postpartum transmission) [15].

Intrauterine transmission:

It is considered as the most important reason for the failure of passive-active immunoprophylaxis in prevention of MTCT. The precise mode of HBV intrauterine transfer is still unknown[16].

a) Serum fluid transmission- It occurs usually in conditions of placenta damage caused by contraction of uterine muscle such as threatened abortion, invasive procedures into the uterus like amniocentesis during pregnancy or specific infections like Toxoplasma, Rubella, Cytomegalovirus and Herpes Simplex infections.

b) Cellular transmission- It refers to transmission of HBV from maternal side to fetal side through placenta cells and transfer the infected peripheral blood mononuclear cell from the circulatory systems of mother to infant.

c) Genetic transmission- When germ cells like oocytes and sperm are susceptible to HBV infection and the virus is passed on to the embryo, this form of transmission occurs.

Intrapartum transmission:

It describes transmission that occurs during childbirth and is regarded as the most significant method of HBV MTCT in the state of nature. When the mother's body fluids or blood pass through the maternal vaginal canal during delivery, the newborn baby may be exposed to HBV-containing bodily fluids or blood[17]. Additionally, if premature labour is imminent, uterine contractions may lacerate the placenta, allowing maternal blood to enter the foetus' bloodstream.

Puerperal transmission:

HBV infection caused by contact with body fluids, blood, breast milk, or other close contacts with the mother after delivery is referred to as puerperal transmission. After universal passive-active immunoprophylaxis of newborns from HBsAg-positive mothers was carried out, it becomes a subordinate to other transmission pathways that are previously discussed because its incidence is minimal.

Strategies for Preventing MTCT of HBV

By preventing MTCT we can reduce the global burden of chronic HBV. On the basis of its mechanism, MTCT of HBV is often prevented. These tactics support prenatal care for women and postpartum care for both moms and their newborns[18].

Immunoprophylaxis provided to newborns:

The incidence of perinatal HBV transmission is apparently decreased by immunoprophylaxis given to newborns. Numerous research, including reviews, have shown that the hepatitis B vaccine with HBIG is more effective at lowering the prevalence of MTCT than the hepatitis B vaccine alone in preventing MTCT of HBV in HBsAg positive women. Infants whose mothers are HBsAg-positive will benefit more from this procedure, according to WHO standards, especially if they are HBsAg-positive themselves. Universal passive-active immunoprophylaxis of infants has significantly reduced the transmission rate of HBV by 85– 95 percent. The Hepatitis B vaccine and HBIG should be administered to newborns of

HBsAg- positive mothers within 12 hours of delivery, according to recommendations from the WHO and the complete process should be completed within 6 months after the baby was born i.e., in the 1st month and at the 6th month respectively. However, infants born to HBsAg-positive mothers must take immunizations, but those born to HBeAg-negative must administer HBIG until the vaccine is proven effective.

Recent studies have demonstrated that giving mothers who were both HBsAg and HBeAg positive three to four doses of the Hepatitis B vaccine without HBIG has an efficacy up to 90%. Also, some studies have shown that vaccination without HBIG can prevent vertical transmission in 66-90% of cases. These reports are useful for alternatively using Hepatitis B vaccine alone with these conditions of HBIG. MTCT of HBV may still occur in 1–15% of newborns from moms who test positive for HBsAg despite the conventional passive-active immunoprophylaxis approach in neonates. Intrauterine infections are a major factor in HBV vaccine failure[19].

Antiviral prophylaxis with nucleoside/nucleotide analogs:

The most significant risk factor for MTCT of HBV is thought to be high HBV DNA levels and HBeAg positive status in pregnant women, as was previously mentioned. Due to the combination of the HBIG and HBV vaccine, the HBV transmission rate in babies born to HBeAg positive mothers is reduced from over 90% to about 3-7%.[20] However, some researchers have revealed that the failure rate of immunoprophylaxis in infants born to mothers with high HBV and HBeAg levels reaches 8–32%. Therefore, reducing maternal HBV DNA levels during pregnancy is the best course of action for preventing MTCT in mothers with high viremia.Telbivudine and tenofovir are two oral anti-HBV medications that have been classified as pregnancy category B medicines. The most effective antiviral medication for treating chronic HBV patients while they are pregnant is lamivudine, which is also the safest option.

Therefore, the most recent treatments for Hepatitis B infection in pregnant women are Lamivudine, Telbivudine, and Tenofovir[21]. Infected pregnant women with HIV have had success using tenofovir. Tenofovir is anticipated to be successful in preventing MTCT of HBV due to its high antiviral activity. Passive-active prophylaxis was administered to all babies. According to newly developed guidelines from the European Association for the Study of the Liver (EASL) and the Asian Pacific Association for the Study of the Liver (APASL), treating pregnant women with high viremia with antiviral drugs like tenofovir or telbivudine at 28–32 weeks of gestation will be both safe and effective in preventing MTCT given in the fig. 1. These findings have shown that pregnant women with high viremia should also receive neonatal immunoprophylaxis. However, there is still a study gap to determine the ideal HBV DNA threshold for antiviral therapy[22].

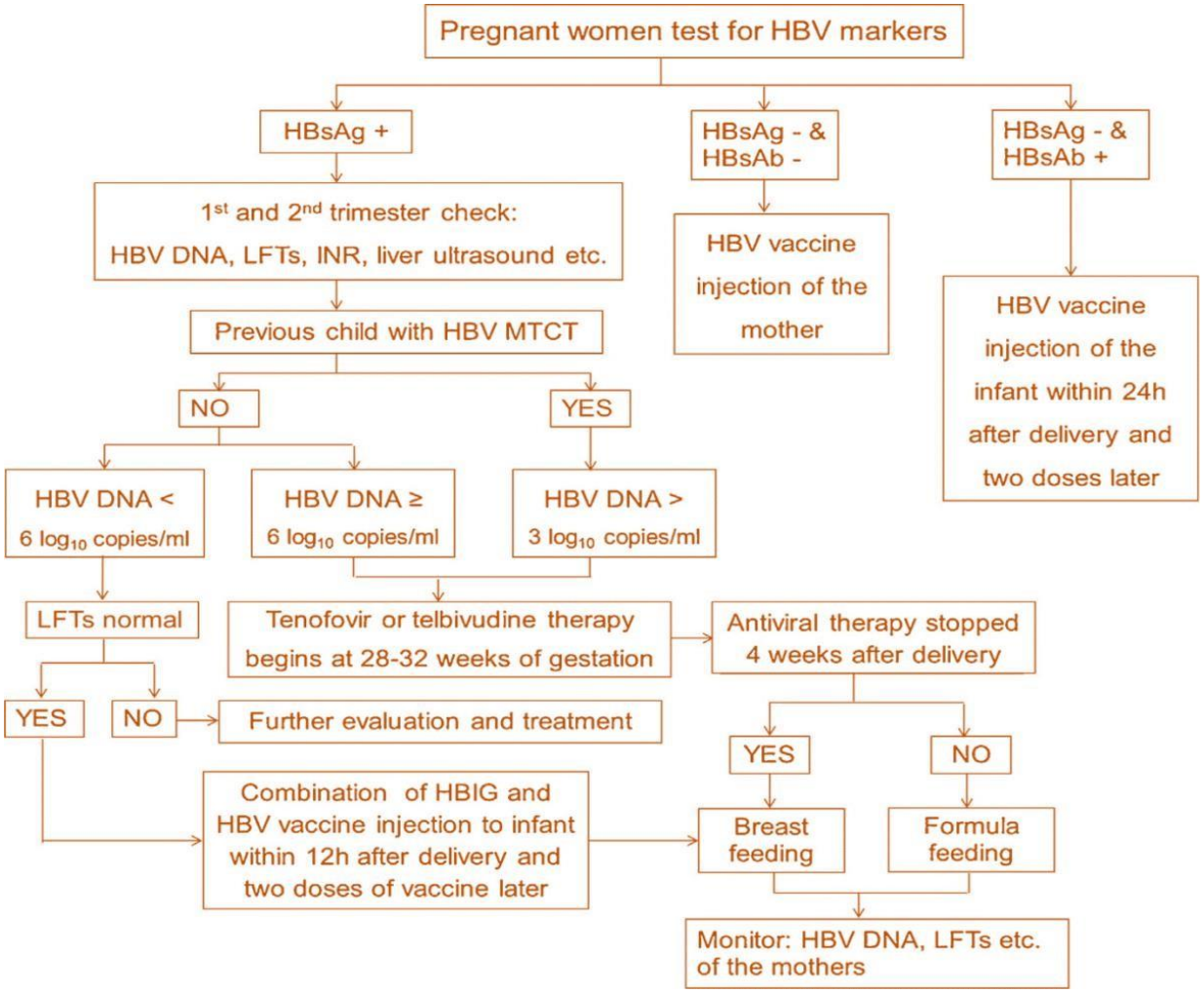

Figure 1: Management of MTCT of HBV in pregnancy. ALT, alanine aminotransferase; HBV, hepatitis B virus; LFT, liver function test; HBsAg, Hepatitis B surface antigen; HBsAb, hepatitis B surface antibody; HBIG, hepatitis B immunoglobulin; INR, international normalized ratio[2].

Periodical administration of HBIG during pregnancy

It is still debatable whether or not pregnant women with HBsAg positivity who get periodic HBIG treatment during the third trimester of pregnancy are able to prevent HBV MTCT. Researchers who hold this opinion think that administering HBIG intramuscularly in numerous small doses will directly neutralise maternal HBV to give passive immunisation. Also, by binding with HBsAg, it might stimulate the immune system and reduce HBV replication to a certain extent. Researchers discovered that in HBV carrier mothers who received HBIG during pregnancy, there was no discernible decrease in maternal HBV DNA. Additionally, none of their newborns tested positive for HBsAb. There was no difference in the prevalence of HBsAb positivity in infants older than 7 months between mothers who received HBIG treatment during pregnancy and those who did not, even in cases where infants' HBsAb was discovered.

Various delivery methods and procedures

The delivery strategy to lower the MTCT of HBV incidence has not yet been determined. In the past it was observed that Infant mucosal membrane contact with maternal fluids or blood during pregnancy was still thought to enhance the risk of HBV MTCT upon vaginal delivery. However, the probability of MTCT of HBV was reduced by caesarean birth[23]. Contrarily, several research came to the opposite conclusion and found no difference between caesarean and vaginal birth in the incidence of MTCT. It was formerly shown that infants delivered via various methods did not have significantly different HBsAg levels after 12 months. There is insufficient evidence to prove that caesarean birth is superior to vaginal delivery in preventing the MTCT of HBV because these results were contradictory. Caesarean delivery is not advised for HBsAg-positive mothers due to the benefits of vaginal delivery and the favorable effects of passive-active immunoprophylaxis on newborns.[24]

Several strategies are being examined to lower the prevalence of HBV infection during labour. Following delivery, the measures include quickly cleansing the neonates' mouths, respiratory tracts, and skin [25]. The likelihood of the foetus being exposed to maternal fluids, serums, and vaginal secretions will be reduced as a result of this process.[26]

Conclusions

The chance to prevent MTCT of HBV presented by HBV infection during pregnancy is not only unique but also significant. The majority of the data is derived from open-labeled and non- randomized retrospective or prospective research because randomised trials are not practical in pregnant women for ethical and other reasons. 90% of babies are successfully protected from MTCT of HBV with the standard passive-active immunoprophylaxis with HBIG plus HBV vaccine in neonates within 12 hours after birth. MTCT of HBV affects up to 9% of newborns as a result of perinatal transmission of HBV linked to high levels of viremia in mothers. For high viremia, it is reasonable to administer antiviral medications such tenofovir or telbivudine. Breastfeeding is recommended in HBsAg-positive mothers, according to standard active- passive immunoprophylaxis regimen. Some topics are still debatable, including whether mothers receiving antiviral therapy should nurse their children, whether pregnant women should receive HBIG injections, and whether antiviral medications may have long-term negative consequences on both HBV-positive mothers and their children.

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