Prevention of Hepatitis B Virus Transmission in Pregnancy

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ABSTRACT

Chronic hepatitis B virus infection is a serious health problem in many countries, particularly in developing countries. In Asia-Pacific region, vertical transmission from mother to child is the main endemicity factor of hepatitis B virus (HBV) infection. Almost 50% cases of hepatitis B virus infection happen during perinatal and neonatal period, including vertical transmission from mother to child during pregnancy.

World Health Organization (WHO), World Gastroenterology Organization (WGO) and many countries have recommended immunoprophylaxis by the administration of hepatitis B vaccine and hepatitis B immunoglobulin (HBIg) to prevent transmission from mother to child. However, there are approximately 10-15% babies born from mother with hepatitis B infected by HBV through intrauterine transmission. Incidence of intrauterine transmission is accounted for around 43-50% if DNA of HBV in the mother is more than 10^7 copies/mL, although passive and active immunization to the baby has been administered. Therefore, administering antiviral drugs in pregnant women with chronic hepatitis B accompanied by immunoprophylaxis is effective in preventing hepatitis B infection transmission during pregnancy, particularly in decreasing the number of virus and administering active or even passive immunization to neonates.

Keywords: *hepatitis B, pregnancy, prevention, transmission*

ABSTRAK

Infeksi virus hepatitis B kronik merupakan permasalah kesehatan yang serius di berbagai negara, terutama di negara berkembang. Di wilayah Asia-Pasifik, transmisi vertikal dari ibu ke anak merupakan faktor utama endemisitas infeksi virus hepatitis B (VHB). Hampir 50% kasus infeksi virus hepatitis B terjadi saat perinatal dan neonatal, termasuk transmisi vertikal dari ibu ke anak saat kehamilan.

World Health Organization (WHO), World Gastroenterology Organization (WGO) dan berbagai negara telah merekomendasikan imunoprofilaksis dengan vaksin hepatitis B dan immunoglobulin hepatitis B (HBIg) untuk mencegah penularan dari ibu ke anak. Namun, masih terdapat sekitar 10-15% bayi lahir dari ibu dengan hepatitis B terinfeksi VHB karena penularan intrauterin. Insidens penularan intrauterin sekitar 43-50% bila DNA VHB ibu lebih dari 10^7 kopi/mL, meskipun dengan imunisasi pasif dan aktif pada bayi. Oleh karena itu, pemberian obat antiviral pada wanita hamil dengan hepatitis B kronik disertai imunoprofilaksis efektif dalam mencegah penularan infeksi hepatitis B saat kehamilan, yaitu dengan menurunkan jumlah virus dan memberikan imunisasi aktif maupun pasif pada neonatus.

Kata kunci: *hepatitis B, kehamilan, pencegahan, transmisi*

INTRODUCTION

Chronic hepatitis B virus infection is a serious health problem in many countries, particularly in developing countries.[1] There are approximately 350 million people in the whole world who suffer from chronic hepatitis B infection. Mortality rate for this disease is around 500.000 to 1.2 million people per year due to hepatitis B infection.[2, 3,4] In Asia-Pacific region, vertical transmission from mother to child is the main endemicity factor of hepatitis B virus (HBV) infection. Almost 50% hepatitis B virus infection cases occur in perinatal and neonatal period, including vertical transmission from mother to child during pregnancy In endemic countries, women in the reproductive age has high positive hepatitis B e antigen (HBeAg) and increases the transmission risk from mother to child, the younger age they were infected, the higher the possibility to become chronic hepatitis B.[1,4,5]

World Health Organization (WHO), World Gastroenterology Organization (WGO) and various countries have recommended immunoprophylaxis by administering hepatitis B vaccine and hepatitis B immunoglobulin (HBIg) to prevent transmission from mother to child. In China, almost 85-90% transmission can be prevented by the administration of both immunoprophylaxis. It has been proved that passive and active immunizations may prevent perinatal and breastfeeding transmission effectively. This also supports the possibility of highest transmission rate during perinatal period. However, there are approximately 10-15% babies born from mother with hepatitis B who are infected with HBV due to intrauterine transmission. Risk of this failure consists of presence of HBeAg and increased titre HBsAg and number of HBV DNA in mothers.[1] Incidence of intrauterine transmission is approximately 43-50% if HBV DNA in the mother is more than 10^7 copies/mL, although passive and active immunizations have been administered to the baby. Therefore, administration of antiviral drugs in pregnant women with chronic hepatitis B along with the immunoprophylaxis is considered effective in decreasing transmission of hepatitis B infection during pregnancy, which is by decreasing viral load and administering active or even passive immunizations in neonates.[1,3,4]

Evaluation and management of pregnant women with chronic hepatitis B is a challenging issue and requires good understanding towards the progress of chronic hepatitis B in pregnancy, particularly if considering antiviral therapy administration.[3,4] Thus, holistic management in pregnant women with chronic hepatitis B is indispensable, with various preventive modalities. This is with one purpose to decrease the transmission rate of hepatitis B virus infection from mother to child that eventually decreases the endemicity of chronic hepatitis B. In this review, we will discuss about four topics, which are influence of hepatitis B in pregnancy, active and passive immunoprophylaxis in neonates, antiviral administration in pregnant women, labour, and lactation.

INFLUENCE OF HEPATITIS B VIRUS INFECTION IN PREGNANCY

Several physiological changes occur during pregnancy, including the increase of metabolism and nutrition consumption. These changes happen to support the needs of pregnant women along with the fetal development. Abundant productions of hormones in pregnant women also need to be metabolized and activated in the liver; also detoxification and metabolism of fetus depend on the mother's liver function. This is related to the previous exacerbation of liver disease and liver injury. There is a tendency for alanine aminotransferase (ALT) to increase in the last trimester and after delivery.[4]

Hepatitis B virus infection will not increase mortality and teratogenic effect in pregnancy. However, there was increase of incidence of babies to be born premature and low birth weight (LBW) in acute infection compared to the general population. Although gestational diabetes mellitus, antepartum bleeding, premature baby and lower Apgar score more often happen in chronic hepatitis B.[2,4] This acute hepatitis B infection need to be differentiated from other acute liver disease in pregnancy, such as intrahepatic cholestasis.[2]

Patients with advanced cirrhosis are usually amenorrhea and infertile due to hypothalamus – pituitary axis dysfunction, but pregnancy may successfully occur in well-compensated cirrhosis. In this case, approximately 50% experienced miscarriages. The main risks for mother are oesophageal varies rupture and bleeding that occurs in 20-25%, particularly in the second trimester and during labour. If the presence of oesophageal varices is known before pregnancy, women who are planning to be pregnant have to be treated first. However, if there are no oesophageal varices, then in the second trimester they are recommended to undergo endoscopy. If oesophageal varices are found, beta-blocker needs to be administered although there is a possible effect to the fetus.[2]

Management of acute varices bleeding in pregnancy include the prompt endoscopy, while administration of vasopressin is contraindicated. Ascites and hepatic encephalopathy need to be treated as usual with diuretic, lactulose, rifaximin, and others. Patients who are known to have big varices, normal delivery is recommended to prevent abdominal surgery.[2]

In pregnancy, there were several modifications of maternal immune system that cause the decrease of immune response to combat hepatitis B virus. The objective of this modification is to prevent fetal rejection, which is allogeneic to maternal immune system. This modification causes the elevated level of HBV DNA and decreased level of transaminase enzymes. After delivery there will be increased of maternal immunity, therefore there will be increase of transaminase enzymes and decrease level of HBV DNA.[2]

Although hepatitis B infection during pregnancy can be well tolerated, but severe hepatitis and failure of liver function induced by inflammation reaction during perinatal may happen. Therefore, the prognosis can be not good.[4]

PROPHYLAXIS WITH IMMUNOGLOBULIN AND VACCINE

Hepatitis virus infection in neonates is defined as the presence of HBsAg 6 months after birth. Anti-HBe and anti-hepatitis B core antigen (anti-HBc) can pass the placenta and usually disappear at the age of 12 and 24 months. The presence of these antibodies is not the marker of infection in babies.[2]

Screening programme in pregnant women with the purpose of identifying the presence of positive HBsAg in pregnant women is a standard programme. In most countries, this programme is routinely performed in pregnant women in the initial prenatal examination. If positive HBsAg is identified, then the babies will receive active and passive immunoprophylaxis at birth to decrease the vertical transmission of hepatitis B. Passive immunization is by administering HBIg, while passive immunization is by administering hepatitis B vaccine.[2,4] Meanwhile, it will be very beneficial if explanation are given to the pregnant women and their family, which include the hepatitis B, ways of transmission (such as through sexual contact, body fluid, blood, or vertical transmission). Screening and vaccination are the keys to success of preventing and controlling HBV infection. Women with hepatitis B should actively plan their pregnancy and evaluate the severity of their disease.[4]

This active and passive prophylaxis administration is effective in preventing transmission, however approximately 10-15% babies are still infected by hepatitis B, particularly those who are born from mother with positive HBeAg.[2,6] HBeAg in mothers may pass through the placenta and induce T cell tolerance in the womb.[2] Transmission of hepatitis B infection may happen in prenatal period, during labour, and early postpartum period. Pregnant women who have been identified to suffer from hepatitis B are advised to be referred to hospitals, which have experience in managing hepatitis B.[4]

Intrauterine hepatitis B infection, which mechanism is still unclear, is the main reason of immunology blockade failure. The high level of HBV DNA in the serum in pregnant women is main risk factor for intrauterine HBV infection to occur. This is strongly associated with the level of HBV DNA and HBeAg titre in placenta blood. This also showed that HBV may infect all types of placental cells (placenta decidua, trophoblast which consists of syncytiotrophoblast and cytotrophoblast, mesenchymal villi, capillary endothelial cells villi). Hepatitis B virus may be found in amnion fluid, breast milk, vaginal fluid and blood in the umbilical cord, with the presence of HBV DNA in these tissues.[2, 7] However, it is still unclear if hepatitis B virus can pass through the placenta by producing trancytosis cells in the first trimester of pregnancy. This virus may pass through trophoblast cells using endosomal transportation system that is still infectious.[7]

HBV DNA is presence in all generation of spermatogenic cell and sperms of males who are infected with HBV, in the follicular fluid and in the ovaries (cellular transfer). The presence of virus in the spermatogenic cell has a role in the transmission of HBV infection to neonates, where there has been homolog sequence of virus between father and child, in discordant partners. The absence of HBeAg in pregnant women is associated with the low viral replication and decreases the risk of intrauterine transmission.[2]

The table below showed the passive or active HBV immunization in term neonates. If mother is HBeAg positive, it is recommended to administer active or even passive immunization in the first 12 hours.[8]

Table 1. Hepatitis B immunization in neonates[8,9]

Mother HBsAg	Immunization	Dose	Schedule (months)	Comments
(+)	Active	EngerixB 10µg/0.5 mL HBVax-II: 5µg/0.5 mL	0, 1, 6	< the first 12 hours
	Passive	HBIg 0.5 mL		< the first 12 hours
(-)/ ?	Active	EngerixB 10µg/0.5 mL HBVax-II: 5µg/0.5 mL	0, 1, 6	Soon after birth

HBVax = Hepatitis B virus vaccine; HBIg = Hepatitis B immunoglobin

ANTIVIRAL THERAPY IN PREGNANT WOMEN

All treatment decision for hepatitis B infection during pregnancy need to consider the risk and benefit for mother and fetus. The main problem associated with mother is the effect of treatment to liver disease, either short term or even long term. While the consideration for fetus is the risk of teratogenic effect in early embryogenesis due to drugs.[2]

In general, basically it is not recommended to initiate antiviral therapy of nucleoside analogue in immunotolerant hepatitis B. Because the risk of intrauterine infection is obviously associated with viremia in the mother, and most of the organs in fetus have developed in the third trimester, thus the strategy of antiviral administration is performed in the last trimester.[1]

Antiviral drug administration along with immunoprophylaxis in pregnant women with chronic hepatitis B is thought to be effective in preventing transmission of hepatitis B infection during pregnancy, which is by decreasing the viral load and administering passive immunization in newborn babies.[10]

Until now, there has still been a controversy regarding the group, which receive the highest benefit from antiviral therapy administration during pregnancy. However, the available guidelines mention that the limit of HBV DNA > 2 x 10^6 IU/mL as an indication of antiviral therapy administration.[11]

Seven drugs which have been approved by Food and Drug Administration (FDA) for hepatitis B therapy are polyethylene glycol (PEG), interferon alpha 2a, interferon alpha 2b, lamivudine, adenoviral, entecavir, telbivudin and tenofovir.[2,10]

Table 1. Categories of antiviral drugs for hepatitis B in pregnancy[2]

Antiviral	Kategori
Lamivudin	C
Entecavir	C
Telbivudin	B
Adefovir	C
Tenofovir	B
Interferon alpha 2b	C
Pegylated-interferon alpha 2a	C

Interferon and peg-interferon are contraindicated during pregnancy due to its proliferative effect.[1] These drugs can be given to reproductive age women with the duration of therapy for approximately 48-96 weeks, but it is recommended to use contraception during therapy.[2] Patients during peg-interferon therapy, who are then pregnant, have to change their therapy with more safe drugs. Pregnant women whose therapy is ceased have risk to experience hepatitis flare, and are recommended to undergo strict monitoring. Similarly, all reproductive age women with HBV infection are recommended to use contraception during therapy and these patients have to informed adverse effects of the therapy during pregnancy.[12]

Oral antiviral drug, nucleoside analogue may inhibit virus proliferation, has been used in long time as hepatitis B antiviral. These drugs also influence the replication of mitochondrial DNA, thus cause the toxicity potency in mitochondria. Based on the safety category for pregnancy, 5 nucleoside analogue drugs are classified as B and C categories. Drugs classified into C category include lamivudine, adefovir, and entecavir. These drugs have teratogenic or embryocidal effect in animals, but there are no studies in human.[2]

Lamivudine has high toxicity in rabbits in the first trimester. However, lamivudine is the first oral antiviral drug that was approved for treatment of hepatitis B, and most clinical experiences indicated the least teratogenic effect in human.[2] Lamivudine for several years have been believed to prevent transmission of intrauterine hepatitis B infection during pregnancy in the last trimester. The preventive effect has also been proven. Although FDA categorized it as a C category drug, in 2009 European Association for the Study of the Liver (EASL) confirmed its safety during pregnancy.[1,13] Although decrease in the number of HBV DNA until undetected status has been reported, lamivudine therapy in the last trimester did not give any guarantee of prevention of transmission of hepatitis B infection from mother to child.[1]

In the study performed by Xu et al using randomized controlled trial (RCT) method, 150 pregnant women with positive HbsAg and high viremia, lamivudine

150 mg was given in 32 weeks pregnancy up to 4 weeks before delivery, where both groups of neonates received HBIg and vaccine at birth. At the age of 1 year old, there were 18% infected babies born from mother receiving lamivudine therapy, while in the control group there were 39% infected babies (p = 0,014).[14] Another meta-analysis study was performed in 10 RCT with the total of 921 pregnant women who received lamivudine therapy, results confirmed the safety and efficacy in preventing intrauterine transmission. However, the disadvantages of this meta-analysis were the presence of heterogeneity of cut off in the number of HBV DNA that received therapy.[1]

Included in the B category are telbivudin and tenofovir. Based on the animal study, there was no teratogenic or embryogenic toxicity risk, but there was no study in human.[2] Toxicology study also demonstrated that telbivudin did not have toxicity in significant organ, genotoxicity, or even mitochondrial toxicity in vitro.[1,15] Tenofovir has high antiviral potency and genetic defence toward resistance, while telbivudin has high antiviral potency but resistance may happen easily.[2]

There are several therapy reports with telbivudin showing fast decrease of serum HBV DNA level. Several reports also showed telbivudin has better clinical efficacy compared to lamivudine in chronic hepatitis B with positive or negative HbeAg.[1,15] In a meta-analysis study conducted by Deng Ming et al, there was 306 pregnant women receiving telbivudin 600 mg therapy in the second or even third trimester up to 1 month after delivery. While in the control group, there were 270 pregnant women who did not receive antiviral drugs. All babies were given HBIg and hepatitis B vaccine at birth. It was concluded that the HbsAg seropositive result or the number of HBV DNA is lower significantly in telbivudin group; both were followed-up at birth and at the age of 6-12 months.[1]

Telbivudin showed good efficacy in suppressing HBV DNA in the third trimester or pregnancy. In a non-randomized study by Han et al in 190 pregnant women with positive HbsAg and positive HBeAg with virus $>10^6$ copies/mL, the efficacy and safety of telbivudin was evaluated and compared to placebo. In both groups, newborn babies received passive or even active immunization within the first 24 hours. Telbivudin administered during 20-32 weeks pregnancy up to 4 weeks after delivery if the disease was not active, but if the disease was chronic active, treatment was continued up to 28 weeks. There was decrease in the seropositivity of HBsAg as much as 6.3% in telbivudin group and 30.4% in placebo group. Twenty eight weeks after delivery, there was significant decrease of HBsAg or even HBV DNA as much as 2% in telbivudin group and 13% in control group. Elevation of ALT postpartum occurred in 7.5% patients receiving telbivudin and 18.5% in placebo group. There was no severe hepatitis happening after the cessation of telbivudin in the fourth week postpartum.[16]

There are limited data regarding the efficacy of tenofovir in pregnant women. Several information regarding the toxicity of tenofovir were obtained from animal study, such as gravid rhesus monkeys, in which there was decreased of *insulin like growth factor* in neonates and inhibited growth in mother with 2 months therapy.[2]

In pregnant women with positive HBsAg, then early pregnancy evaluations are recommended. This includes the evaluation of HBsAg, HBeAg, anti-HBe, HBV DNA, activity of hepatitis and severity of fibrosis or liver cirrhosis.[2,4,17] In patients with high level of HBV DNA and active hepatitis (ALT <2 times upper normal limit, HBV DNA VHB $>10^5$ copies/mL) in the early or even in the presence of liver cirrhosis, but antiviral need to be given at the start of pregnancy. For patients with normal liver function, ALT and HBV DNA need to be re-evaluated in mid-pregnancy (26-28 weeks). Patients with HBV DNA $>10^7$ copies/ mL or before delivering baby with positive hepatitis B and HBV DNA $>10^6$ copies/mL, then antiviral therapy (lamivudine, tenofovir or telbivudin) should be given in 28-30 weeks up to 4 weeks after delivery. Further, it has to be determined if the aforementioned therapy will be continued or not based on the patient's condition. ALT and HBV DNA level need to be monitored in all pregnant women with positive HBsAg in the 1,3, and 6 months after delivery. Presence of hepatitis flare, HBeAg seroconversion, and changes of positive anti-Hbe have to be detected. Active and passive immunization need to be given to all newborn babies as scheduled, HBV-M (HBsAg, HBeAg, anti-HBe) and HBV DNA level also need to be detected at birth and first 7 months. In patient who has been diagnosed with liver cirrhosis before pregnancy, antiviral therapy need to be administered first; one of these drugs need to be continued during pregnancy with close monitoring.[2, 4]

LABOR AND LACTATION

In the survey performed by Guo et al, from 158 pregnant women with positive HBsAg approximately 82% underwent caesarean delivery to prevent direct contact with blood or other body fluid. This is

performed to decrease HBV transmission from mother to child. Several studies stated that caesarean delivery could decrease HBV transmission from mother to child. However, several other studies found that there was no significant difference of HBV transmission between caesarean delivery and vaginal delivery.[19]

Meta-analysis from 4 randomized studies, which involved 789 pregnant women, evaluated the efficacy and safety of caesarean delivery (caesarean delivery before labour or before placental membrane rupture) compared with vaginal delivery in preventing hepatitis B transmission from mother to child. It was obtained that caesarean delivery has high transmission rate, approximately 10.5% and vaginal delivery 28% (p = < 0.000001). There was no data regarding mother morbidity or child based on way of delivery. However, conclusion of the meta-analysis needs to be interpreted with caution considering the high risk of bias in all studies including in the analysis. Therefore, the role of caesarean delivery in preventing transmission of hepatitis B virus infection from mother to child is uncertain.[2] Currently, there is no data, which convince that caesarean delivery, decrease the transmission of HBV infection from mother to child compared to vaginal delivery.[2,18]

Based on this information, it is important for doctors to decide whether or not to perform caesarean delivery, considering that caesarean delivery also increase maintenance cost, lengthening hospital stay, and may cause surgical complications.[19]

Before the availability of neonatal immunization, study reported hepatitis B infection in newborn babies from positive HbsAg mother as much as 53% who were given breast milk and 60% were given formula milk. By immunoprophylaxis administration, babies who were given breast milk have transmission risk of 0% and formula milk 3%. Latest guidelines stated that breast milk administration is not contraindicated in mother with hepatitis B virus infection who is not receiving antiviral therapy and their babies receiving immunoprophylaxis. In mother who are consuming therapy with lamivudine or tenofovir, breast milk administration is not recommended, due to the less data available regarding antiviral safety in lactating patients, although tenofovir can be detected in breast milk in low concentration.[2, 4,12]

CONCLUSION

In preventing transmission of hepatitis B infection in pregnancy, examination of HbsAg is recommended in all pregnant women, without considering previous results of examination or vaccination history. Pregnant women with high hepatitis B virus level has high risk of transmitting infection to the baby, although active or even passive prophylaxis have been given, therefore in this condition administration of antiviral therapy during the third trimester need to be considered. Breastfeeding is not contraindicated in women with hepatitis B infection, except in the administration of antiviral therapy, there is no clear evidence that caesarean delivery decreases transmission risk from mother to child compared to normal delivery.

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