Journal of Clinical Virology 77 (2016) 32–39

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Review

Management of mother-to-child transmission of hepatitis B virus: Propositions and challenges

Panpan Yi, Ruochan Chen, Yan Huang, Rong-Rong Zhou*, Xue-Gong Fan*

Department of Infectious Diseases, Key Laboratory of Viral Hepatitis of Hunan, Xiangya Hospital, Central South University, Changsha 410008, China

ARTICLE INFO

Article history:
Received 10 October 2015
Received in revised form 26 January 2016
Accepted 4 February 2016

Keywords:
Hepatitis B virus
Mother to child transmission
Immunoprophylaxis
Antiviral therapy
Breastfeeding

ABSTRACT

Chronic hepatitis B virus (HBV) infection due to mother-to-child transmission (MTCT) during perinatal period remains an important global health problem. Despite standard passive–active immunoprophylaxis with hepatitis B immunoglobulin (HBIG) and hepatitis B vaccine in neonates, up to 9% of newborns still acquire HBV infection, especially these from hepatitis B e antigen (HBeAg) positive mothers. Management of HBV infection in pregnancy still need to draw careful attention because of some controversial aspects, including the failure of passive-active immunoprophylaxis in a fraction of newborns, the effect and necessity of periodical hepatitis B immunoglobulin (HBIG) injection to the mothers, the safety of antiviral prophylaxis with nucleoside/nucleotide analogs, the benefit of different delivery ways, and the safety of breastfeeding. In this review, we highlight these unsettled issues of preventive strategies in perinatal period, and we further aim to provide an optimal approach to the management of preventing MTCT of HBV infection.

Contents

Abbreviations: HBV, hepatitis B virus; HBI, Ghepatitis B immunoglobulin; MTCT, mother to child transmission; HCC, hepatocellular carcinoma; HBIG, hepatitis B immunoglobulin; HBsAg, hepatitis Bs antigen; HBeAg, hepatitis Be antigen; WHO, World Health Organization; PBMC, peripheral blood mononuclear cell; EASL, European Association for the Study of the Liver; APASL, the Asian Pacific Association for the Study of the Liver; AASLD, American Association for the Study of Liver Diseases (AASLD).

* Corresponding authors at: Department of Infectious Diseases, Key Laboratory of Viral Hepatitis of Hunan, Xiangya Hospital,Central South University, Changsha 410008, China. Fax: +86 731 8432 7332.
E-mail addresses: rr_xy1234@126.com (R.-R. Zhou), xgfan@hotmail.com (X.-G. Fan).

http://dx.doi.org/10.1016/j.jcv.2016.02.003

1. Introduction

Chronic hepatitis B virus (HBV) infection is an important global health problem. According to World Health Organization (WHO) estimates, more than 240 million people worldwide are chronically infected with HBV [1,2]. Most of them acquire their infections during the perinatal period or in early childhood, especially in highly endemic areas [3–5]. Even in areas with low endemicity, perinatal or early childhood transmission may account for more than one third of chronic infections [1,2,6]. According to previous studies [1,3,7], newborns have 90% chance to become chronic carriers after infection with HBV and in children less than 3 years old the chance is up to 50%, but in adults the chance is only 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. In China, the rate of HBV infection among women of childbearing age is still at a high level (7.18%) [8], indicating that women of childbearing age with chronic HBV infection remain a crucial source of HBV transmission. Therefore, effective preventing MTCT of HBV from pregnant women to their newborns within the perinatal period is a promising efficient approach to interrupt chronic HBV infection [7].

Based on the mechanisms of MTCT of HBV, several strategies have already been invited for the prevention of HBV infection during perinatal period. HBV vaccination has been adopted in the national immunization program in China and many other countries, and administration of vaccination combined with hepatitis B immunoglobulin (HBIG) within 12 h after birth has been applied as standard procedures for newborns from HBV positive mothers [2]. Nucleoside/nucleotide analogs have proved to be useful and relatively safe in reducing the incidence of MTCT in pregnant women with high HBV DNA load [2,9]. These efforts decreased the incidence of carrier rate dramatically in the past years. However, it is still far away from completely eradicating MTCT of HBV because of small part of individuals (around 10%) with intrauterine infection and immunoprophylaxis failure [7,9].

Management of HBV infection in pregnancy is difficult because of several peculiar and somewhat controversial aspects. These challenges include: (1) the failure of passive-active immunoprophylaxis in a small part of newborns, (2) the effect and necessity of periodical HBIG injection to the mothers, (3) the safety of antiviral prophylaxis with nucleoside/nucleotide analogs, (4) the benefit of different delivery ways, (5) the safety of breastfeeding. This review will focus on these issues and provide an optimal approach to the HBV management of preventing MTCT.

2. Mechanisms of MTCT of HBV

Understanding the mechanisms of MTCT is essential for the management of chronic HBV infection, we will briefly discuss it first. Perinatal transimission has been recognized as the main mode of HBV transmission. There are three possible routes of transmission: transplacental transmission of HBV in utero (intrauterine transmission), natal transimission during delivery (intrapartum transmission) and postnatal transmission during care or through breast milk (postpartum transmission) [7,10,11].

2.1. Intrauterine transmission

Intrauterine transmission of HBV is considered to be the most important reason for the failure of passive-active immunoprophylaxis in preventing MTCT [7,9]. Different diagnostic criteria [12–20] had been applied for the diagnosis of HBV intrauterine infection. Since there is no consensus on the diagnosis criteria of HBV intrauterine infection, different proofs that could identify the existence of HBV components in serum of newborns had been used (Table 1). The exact mechanism of intrauterine transmission of HBV remains to be illuminated. The most frequently mentioned hypotheses involve: (a) serum/body fluid transmission, which usually occurs in conditions of placenta damage caused by contraction of the uterine muscle such as threatened abortion [21], invasive procedures into the uterus like amniocentesis during pregnancy [22] or specific infections like TORCH (Toxoplasma, Rubella, Cytomegalovirus and Herpes Simplex) infection; (b) cellular transmission, which refers to transmission of HBV from the maternal side to the fetal side through placenta cells and transfer of infected peripheral blood mononuclear cell (PBMC) [15] from the maternal circulation system into the fetal circulation system; and (c) genetic transmission, germ cells like sperm and oocytes could be infected by HBV and transferred the virus to the embryo [23,24].

Accumulated proofs have identified that high serum HBV DNA levels and HBeAg positive status in pregnant mothers are key factors for indicating the increased risk of MTCT of HBV, especially in intrauterine transmission of HBV through villous capillary endothelial cells [25–27]. Wiseman et al. [28] have shown a transmission rate of 9% for newborns born from mothers with virus load > 8 $\log_{10}$ copies/ml (7.3 $\log_{10}$ IU/ml) despite standard passive-active immunoprophylaxis administration and no transmission below this cut-off. Recent studies even proposed a lower level of 6 $\log_{10}$ copies/ml (5.3 $\log_{10}$ IU/ml) of maternal viremia as the cut-off [29,30] and the reported rate [15,31] of MTCT of HBV to newborns ranged from 8% to nearly 30% if maternal HBV DNA levels are higher than 6 $\log_{10}$ copies/ml (5.3 $\log_{10}$ IU/ml).

HBeAg positivity is another independent risk factor for the MTCT of HBV. In fact, HBeAg can pass through the placenta via partial placental leakage or via the “cellular route”. The absence of HBeAg expression is associated with lower levels of viral replication and with a significantly lower risk of intrauterine transmission of HBV. [32] These data presume that antiviral therapy with nucleoside/nucleotide analogs can decrease viral loads of HBV, which may be effective to reduce the risk of intrauterine transmission. In addition, perinatal infection with the immunoprophylaxis occurred in 0.4% (0.0–2.5%) in infants born to HBeAg-negative-carrier mothers [33]. And previous studies have suggested that anti-HBe-positive women infect their infants only if they have high HBV viremia levels [34], and HBV mutants in the precore and/or core regions in some anti-HBe-positive carrier mothers, leading to be unable to synthesize the HBeAg, may transmit fulminant hepatitis B to their infants [35–38]. However, the role of precore and/or core mutation is not very well documented in MTCT.

2.2. Intrapartum transmission

Intrapartum transmission refers to transmission occurring during childbirth and it is recognized as the most important route of HBV MTCT in the state of nature. During the process of delivery, newborns may have the chance to be exposed to maternal body fluids or blood that contains HBV at the time when they pass the maternal genital tract [9]. And also in case of threatened preterm labor the contractions of the uterus may cause the laceration of the placenta and subsequently resulting in entering of maternal blood into fetal circulation [7].

2.3. Puerperal transmission

Puerperal transmission means infection of HBV due to contact with maternal breast milk, body fluids, blood or other close contacts between newborns and mothers after delivery [7,9]. It is subordinate to other transmission routes mentioned before for its incidence is very low after universal passive-active

Table 1
Diagnosis criteria of HBV intrauterine infection.

Reference	Diagnosis criteria
Chau et al. [13] and Goudeau et al. [12]	Persistent serum anti-HBc IgM positive after birth
Beasley et al. [14]	High titers of HBsAg within 24 h of birth and after the completion of HBIG and vaccine immunoprophylaxis
Xu et al. [15]	Pre-S1 protein positive in umbilical blood
Li et al. [16]	HBsAg and/or HBeAg positive, or HBV DNA positive in neonatal peripheral blood
Vermeulen et al. [17]	Peripheral blood HBV DNA positive
Zhang et al. [18]	HBsAg positive within 24 hours, and/or 1 month, followed by HBsAg positive at 6 months
Zhang et al. [19]	HBV DNA or HBsAg detectable in peripheral serum samples of infants at 52 weeks
Xu et al. [20]	Positive for HBsAg, HBV DNA in serum, or HBV DNA in PBMCs tested within 24 h after birth

immunoprophylaxis of newborns born from HBsAg positive mothers was performed.

3. Strategies for preventing MTCT of HBV

Prevention of MTCT of HBV is based on its mechanisms. The strategies include the treatments for mothers during pregnancy and efforts for both newborns and their mothers after birth.

3.1. Immunoprophylaxis provided to newborns

Immunoprophylaxis provided to newborns clearly reduces the incidence of perinatal HBV transmission. With the administration of infant universal vaccination, the incidence of HBsAg declined from 9–12% to <1% in China [39]. Many studies including Cochrane systematic reviews indicate that vaccination alone is insufficient to prevent MTCT of HBV in these HBsAg positive mothers, while combination of Hepatitis B vaccine with HBIG has been proved to be more efficient in reducing MTCT prevalence than vaccine or HBIG alone [40–43]. WHO guidelines also stated that HBIG conjunct with vaccination may be of additional benefit for infants from mothers who are HBsAg-positive, particularly if they are also HBeAg-positive [44]. The transmission rate of HBV has decreased 85–95% by universal passive and active immunoprophylaxis of newborns [30]. Thus, WHO and most guidelines suggested that newborns from HBsAg positive mothers should receive both HBIG and Hepatitis B vaccine within 12 h after delivery, and the complete immunoprophylaxis process also includes at least two more doses of HBV vaccine at 1 month and 6 month after birth [42,45,46].

Howerve, whether it is necessary for infants born from HBsAg positive but HBeAg negative mothers to apply HBIG with vaccine remains to be established. Data from a recent systematic review and meta-analysis show that vaccine alone seems to be equally effective to the combination of HBIG and vaccine for neonates of HBsAg-positive and HBeAg-negative mothers in preventing MTCT of HBV infection [47]. More evidences are needed to warrant on the addition of HBIG to vaccine for infants of HBsAg-positive but HBeAg-negative mothers. So far, WHO guidelines stated that, protection against MTCT achieved by immediate vaccination against HBV may not be significantly improved by the addition of HBIG, in full-term neonates whose mothers are HBsAg-positive but HBeAg-negative [44].

In addition, HBIG may not be feasible in most settings, due to concerns related to supply, safety and cost. Studies have showed that administration of a 3 or 4 dose series of hepatitis B vaccine without HBIG has a protective efficacy of 70–95% in mothers who were both HBsAg and HBeAg positive [14,48,49]. Some studies have shown that when HBIG is unavailable, vaccination alone can prevent vertical transmission in 66–90% of cases [50]. A systematic review found vaccination reduced the occurrence of hepatitis B (risk ratio 0.28, 95% confidence interval 0.20–0.40), compared with placebo or no intervention [41]. These findings are supportive to alternatively use Hepatitis B vaccine alone in settings where financially constraints the use of HBIG.

Despite standard passive-active immunoprophylaxis regimen in neonates, MTCT of HBV may still occur in 1–15% of children born from HBsAg-positive mothers, especially those carrying HBeAg [4,43,51–53]. One of the great causes of vaccine failure is related to intrauterine infection [51,54,55]. Reasons for the failure of HBV vaccine in stimulating the host to produce specific antibodies against HBV are complicated and not yet clearly elucidated. The factors involved include: (1) the immune tolerance caused by low levels of HBV infection before injection of HBV vaccine and this usually happens in uterus during pregnancy [56]; (2) the mutation of HBV S gene [57]; (3) low activity of IL-2 and related deficiency of immune functions [58,59]; (4) HLA hereditary types and the genes correlated with unresponsiveness of HBV vaccine are HLA-DP, HLA-DQ and HLA-DR [60]; (5) Deficiency of vaccines. The present Hepatitis B vaccine of multidose prolonged regimens remains some persons who fail to achieve adequate protection. While, recombinant vaccine containing S, preS1 and preS2 antigens could significantly increase reaction rates of HBV vaccine [61].

3.2. Antiviral prophylaxis with nucleoside/nucleotide analogs

As previously mentioned, high HBV DNA level and HBeAg positive status in pregnant women are considered as the most important risk factors for MTCT of HBV. The HBV transmission rate in newborns born from HBeAg positive mothers has decreased from >90% to approximately 3–7% by the combination of HBIG and HBV vaccine administration [14,41,62,63]. However, other studies show that the failure rate of immunoprophylaxis in newborns born from mothers with HBeAg positive and high HBV reaches to 8–32% [28,64,65]. Thus lowering the level of maternal HBV DNA during pregnancy is momentous for the prevention of MTCT in mothers with high viremia.

Among the current oral anti-HBV drugs, telbivudine and tenofovir have a pregnancy category B designation. Lamivudine has been successfully used in preventing MTCT of HIV in pregnant women for a relatively long time and proved to be a safe agent during pregnancy although it carries a pregnancy category C classification. Thus, lamivudine, telbivudine and tenofovir are currently available options for pregnant mothers with HBV infection. Plenty of studies have been explored the possibility of antiviral therapy in reducing MTCT of HBV in mothers with high serum HBV DNA levels during the second or third trimester of pregnancy based on standard passive–active immunoprophylaxis of newborns [32].

Lamivudine is the longest used antiviral drugs in the treatment of pregnant chronic hepatitis B patients. In 2009, a large randomized, double-blind placebo-controlled trial was performed to evaluated the efficacy of lamivudine administration to prevent MTCT in pregnant women with HBeAg positive and HBV DNA > 9 $\log_{10}$ copies/ml (8.3 $\log_{10}$ IU/ml) from week 32 of gestation to week 4 postpartum [64]. All newborns received standard passive-active immunoprophylaxis. For a major problem of loss to follow-up, data showed only a trend but no significant difference in the prevalence of MTCT (6% lamivudine vs. 12% placebo, $p = 0.37$) [64]. However, Yu et al. [66] also explored the efficacy and

safety of lamivudine in 100 pregnant women with HBeAg positive and HBV DNA levels >7 $\log_{10}$ copies/ml (6.3 $\log_{10}$ IU/ml) at week 24–32 of gestation. All neonates were also administrated standard passive–active immunoprophylaxis. Result showed that the MTCT rates were 0% and 7% in lamivudine group and control group respectively ($p < 0.05$). However, a recent observational study in Australia suggested that a low barrier to resistance of lamivudine also can be observed as lamivudine administration started in the third trimester of pregnancy and stopped shortly after delivery [67]. In the study, 21 women with high viral load of >7 $\log_{10}$ IU/ml were treated with lamivudine for an average duration of 53 days. At the end of treatment, the median decrease in viral load was 2.6 $\log_{10}$ IU/ml, but HBV-DNA remained >7 $\log_{10}$ IU/ml in 18% of cases. Notably, viral variants with reduced sensitivity to lamivudine were observed in 4 women (19%). Therefore, lamivudine administration during the third trimester has poor antiviral activity with a risk of selecting resistance mutations. Currently lamivudine is no longer a first-line option for the treatment of chronic hepatitis B patients because of the high resistant rate. Thus, its application in pregnant women during the third trimester of pregnancy should be carefully assessed for the same reason.

Compared with lamivudine, telbivudine is a newly developed anti-viral agent that has higher efficacy and resistance barrier [68–70]. A large prospective open label study with 229 HBV DNA >7 $\log_{10}$ copies/ml (6.3 $\log_{10}$ IU/ml) and HBeAg-positive pregnant women was carried out in China [71]. One hundred and thirty-five mothers received telbivudine from 20–32 weeks of gestation to 1 month postpartum or continuous treatment after delivery if necessary, while 94 mothers served as controls. All infants received standard passive–active immunoprophylaxis. Prior to delivery, all telbivudine-treated mothers obtained a more than 3 $\log_{10}$ copies/ml decline of the viral load, whereas HBV DNA levels in untreated mothers remained unchanged. The incidence of HBsAg-positive neonates at 7 months of age was 0% in the telbivudine arm compared to 8% in untreated arm ($p = 0.02$). A later meta-analysis that evaluated 6 trails with a total of 576 pregnant women showed that telbivudine administrated in late pregnancy is effective in reducing MTCT, and no significant adverse effects were observed [72]. However, this study only enrolled 2 randomized controlled trials with a limited sample size. In a recent well organized observational study in China, 252HBeAg-positive mothers with HBV DNA >6 $\log_{10}$ copies/ml (5.3 $\log_{10}$ IU/ml) received telbivudine at gestation week 28 until postpartum week 4 and 345 mothers with matched characteristics but without antiviral agents served as controls [19]. The rate of MTCT in the telbivudine treated group is 0% vs. 2.84% in the untreated group ($p = 0.002$). Other data from several latest studies carried out in China [73,74] similarly support that telbivudine significantly reduces vertical transmission of HBV without evident adverse effects. However, high quality, large-sized and randomized controlled trials are needed to confirm efficacy and safety of telbivudine administration in high viral load mothers in late pregnancy to prevent MTCT of HBV.

Tenofovir has been safely used in pregnant women with HIV infection [75]. Based on its high antiviral activity, high barrier to resistance and safety, tenofovir is expected to be effective in preventing MTCT of HBV [76]. In a retrospective study, 21 of 45 enrolled HBeAg-positive pregnant women with HBV DNA > 7 $\log_{10}$ copies/ml (6.3 $\log_{10}$ IU/ml) were treated with tenofovir from week 18–27 of gestation, and 24 of them were untreated as controls [77]. All newborns received combined passive–active prophylaxis. The rate of MTCT of HBV in the treated groups was 0% compared to 8.3% in the untreated controls ($p = 0.022$) and no significant adverse effects were observed. In recent years several prospective studies about efficacy and safety of tenofovir in pregnant women were conducted. Greenup et al. [78] enrolled 58 pregnant women taking tenofovir from 32 weeks of pregnancy till 4–12 weeks after delivery and 20 pregnant women receiving no intervention as controls. Tenofovir significantly reduced maternal viral load with a mean reduction of 3.64 ± 0.9 $\log_{10}$ IU/ml and dramatically decreased incidence of MTCT of HBV at delivery. The rate of MTCT was 2% in tenofovir group compared with 20% in control group. The limitation of this study is the high loss of follow-up rates in newborns (50% in control and 24.1% in tenofovir group). A better organized prospective multi-center trial carried out in Taiwan by Chen et al. [79] enrolled 118HBsAg- and HBeAg- double positive pregnant women with high HBV DNA load of >7.5 $\log_{10}$ IU/ml. Among these mothers, 62 received tenofovir from 30–32 weeks of pregnancy till 1 month after delivery and 56 received no antiviral agent served as control group. Tenofovir treatment distinctly decreased maternal HBV DNA levels and reduced perinatal transmission rate. At delivery, maternal HBV DNA was 4.29 ± 0.93 $\log_{10}$ IU/ml (vs. 8.10 ± 0.56 $\log_{10}$ IU/ml in control group, $p < 0.0001$) and HBV DNA positivity rate in newborns was 6.15% (vs. 31.48% in control group, $p = 0.0003$). HBsAg positive rate in 6 months old infants in tenofovir group was 1.54% (vs. 10.71% in control group, $p = 0.0481$). Due to its effectiveness and good tolerability, tenofovir is promising to be considered to be one of the first-line options for pregnant women with high levels of HBV DNA.

Although report from the antiretroviral pregnancy registry (APR) [80] and other studies suggested that the overall risk of major birth defects of newborns in lamivudine and tenofovir treated mothers is similar to the general population, to date no long-term infant growth data are available. Lamivudine has been used in pregnant women for the longest time and more safety data were accumulated. According to APR data, lamivudine taken in the first trimester resulted in a 1.5-fold increase in risk of overall major birth defects. For the use of emtricitabine and tenofovir in the same period during pregnancy, the risk of birth defects would be at least 2-fold than general population [80,81]. The first and the second trimester are more important than the third trimester for the development of fetal organs, so the initiation of anti-viral therapy is recommended in the third trimester that helps to minimize the effect of these drugs to fetal development. Entecavir and tenofovir are more effective and have a higher barrier of resistance. But currently studies about the safety of entecavir in pregnant HBV DNA positive women and their offspring are unavailable. The potential toxicity of these antiviral agents and its effect on the growth of exposed newborns and pregnant women still need further large, long and appropriately designed clinical studies. For these concerns, the American Association for the Study of Liver Diseases (AASLD) concludes that more safety data are required before administration with these anti-viral drugs for the prevention of MTCT of HBV could be recommended [82].

Based on the accumulated findings, for the pregnant women with high viremia, new guidelines from the European Association for the Study of the Liver (EASL) and the Asian Pacific Association for the Study of the Liver (APASL) indicate that, in addition to neonatal immunoprophylaxis, treating with antiviral agents such as tenofovir or telbivudine during pregnancy beginning at 28–32 weeks of gestation may be safe and effective in preventing MTCT [83]. However, there is still a research gap to determine the optimal threshold of HBV DNA for antiviral therapy. As previously described, a viral load of HBV DNA > 6 $\log_{10}$ copies/ml (5.3 $\log_{10}$ IU/ml) has been regarded as the main risk of perinatal transmission, and the transmission risk increases with a prior child with passive–active immunoprophylaxis failure [31,84,85]. Thus, we recommend antiviral therapy may be applied for pregnant women with HBV DNA > 6 $\log_{10}$ copies/ml (5.3 $\log_{10}$ IU/ml) or with previous child who occurred perinatal transmission after passive–active immunoprophylaxis failure (Fig. 1). In addition, it is also unsettled to determine the risk of exacerbation or post-partum flare in the mothers after cessation of antiviral therapy, as well as

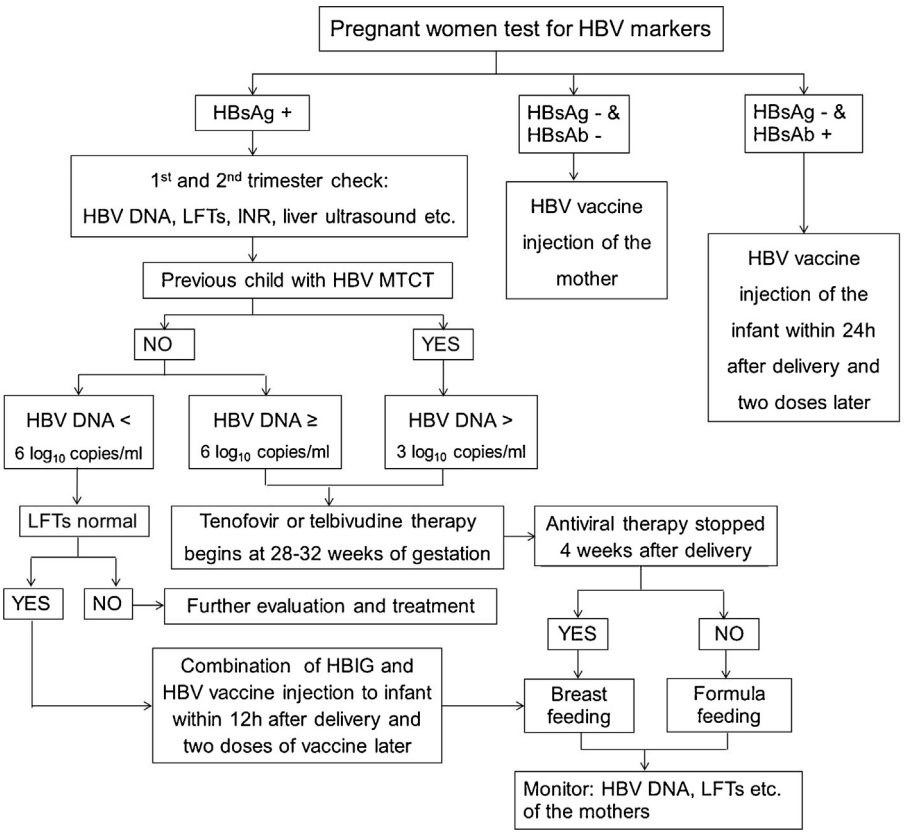

Fig. 1. Management of MTCT of HBV in pregnancy. HBsAg, Hepatitis B surface antigen; HBsAb, hepatitis B surface antibody; ALT, alanine aminotransferase; HBV, hepatitis B virus; LFT, liver function test; INR, international normalized ratio; MTCT, mother to child transmission; HBIG, hepatitis B immunoglobulin.

to establish the optimal duration of continuation of therapy post partum (4 weeks or 12 weeks). Thus, WHO recently proposes that antiviral therapy would be for a limited period for the purpose of reducing MTCT. If a woman requires treatment based on her own clinical condition then that treatment would be continued through the pregnancy [44]. Discontinuation of therapy at any point during or after pregnancy should require serially monitoring of ALT and HBV DNA levels due to the potential for flares upon withdrawal [31,84,85].

3.3. Periodical HBIG administration during pregnancy

Whether periodical HBIG administration during the third trimester of pregnancy in asymptomatic HBsAg positive pregnant women impacts on preventing MTCT of HBV or not is controversial. Researchers who support the viewpoint believe that multiple small doses of intramuscular HBIG injection could provide passive immunization by neutralizing maternal HBV directly. What's more, it could activate the immune system by binding with HBsAg and results in decreasing HBV replication and HBV DNA load to a certain extent. This will subsequently reduce the prevalence of HBV in newborns and/or increase their HBsAb positive rate. Several studies in China [27,86] and some meta-analyses [87,88] supported the use of HBIG during pregnancy. However these meta-analyses had limitations that they ignored the random principle or the imbalance of HBeAg status in the involved pregnant women as well as the serious heterogeneity involving study qualities, patients' infectious status or dosages of HBIG [4,89].

Subsequent studies and meta-analyses produced divergent results. [43] They found no significant decrease in maternal HBV DNA after the administration of HBIG in HBV carrier mothers during pregnancy. In addition, none of their infants was HBsAb positive [90]. Even in studies in which infants' HBsAb were detected, there was no difference in HBsAb positive rate in infants at more than 7 months of age between mothers with or without HBIG intervention during pregnancy [89,91]. The possible reasons for not using periodical HBIG administration during pregnancy include: (1) the half-life of HBIG is short, therefore, its neutralization efficacy is limited and transient [92]. (2) Small dosage of HBIG injection (200 IU or 400 IU) is invalid in decreasing maternal HBV load and insufficient for HBIG to enter the fetal circulation. Although experience from liver transplantation patients suggested that a continuous serum concentration of 100–500 IU/l of HBIG is sufficient for the neutralizing of HBV in the blood [92], in liver transplanted patients the infected liver had been replaced by a HBV negative one and they were given very large doses of HBIG, which is quite different from the conditions of these pregnant mothers. (3) Massive HBIG injection may cause HBV mutation, leading to immune resistance to HBV strains [9,89]. This will subsequently result in the failure of passive–active immunoprophylaxis and increased resistance of mutative virus to antiviral agents. Consequently, the periodic administration of HBIG to the mother to prevent vertical transmission is currently not recommended. [42] More qualified data are needed to demonstrate the effect of HBIG injection during pregnancy.

3.4. Different delivery ways and procedures in delivery

The delivery way to maximumly reduce the incidence of MTCT of HBV remains controversial. In the past, vaginal delivery was considered to increase the chance of HBV MTCT, for infant mucosal membrane directly contacts with the maternal fluids or blood. This hypothesis is supported by recent studies [93]. Guo et al. [94] showed that cesarean delivery decreased the risk of MTCT of

HBV. On the contrary, other studies concluded that there is no difference in the incidence of MTCT between cesarean and vaginal delivery. One study observed HBsAg-positive mothers' infants for a relatively long time and found that at 12 months after birth the HBsAg levels of infants with different delivery ways were not distinct [95]. Since these results were conflicting, there is not enough evidence to support that cesarean delivery is better in avoiding MTCT of HBV compared with vaginal delivery. In view of many benefits of vaginal delivery compared with cesarean delivery and the approving effects of passive-active immunoprophylaxis in newborns, cesarean delivery is not recommended in HBsAg-positive mothers. Elective cesarean delivery is suggested to be started before the onset of labor and rupture of membrane if it has to be chosen for other reasons in order to avoid possibility of transmission in HBsAg-positive mothers.

Several measures are considered to be available to reduce the infection rate of HBV in labor. These measures include early and quick cleaning of the respiratory tract, mouth and skin of the newborns after delivery. This process will decrease exposure chance of fetus to their maternal amniotic fluid, serum and vaginal discharges [95]. Also procedures that may damage the integrity of fetal skin, like blood sampling, should be avoided.

4. Safety of breastfeeding in MTCT of HBV

Currently, the presence of HBsAg, HBeAg and HBV DNA in breast milk is confirmed. However, plenty of studies indicated that based on implementation of immunoprophylaxis, breastfeeding of infants by HBsAg-positive mothers has no additional risk to MTCT of HBV infection [42,52,96–99]. Hill et al. [96] reported that breastfeeding of infants by HBsAg-positive mothers did not increase the infection rate of HBV compared with formula feed infants. A meta-analysis of 1624 infants supported that breastfeeding did not increase the risk of MTCT [100]. In a recent multi-center study in China [25], 1186HBsAg-carrier mothers and their infants aged 8–12 months were followed, yielded a same conclusion. In a recent study, exposure to a larger amount of HBV infectious particles via breast milk was detected, but the child correctly vaccinated was not infected with HBV, indicating breastfeeding may not be a contraindication in HBV-positive mothers after standard immunoprophylaxis of their infants [101]. It was supported by current guidelines [7,44,102–104].

However, little is known about the effects on the infant of exposure to NAs during breastfeeding [101,102]. Guidelines from EASL and other organizations deem that the safety of nucleoside/nucleotide analogs therapy during lactation is uncertain [84,103]. Since breastfeeding is advantageous, especially in low-income countries where HBV is highly endemic, this recommendation is thorny. Nonetheless, it is somewhat counterintuitive and controversial, in light of the fact that the chance for exposure of infants to drugs in utero are likely higher than that through breast milk, but these drugs are recommended for use during pregnancy. Moreover, WHO guidelines state that HIV infected women could continue antiretroviral treatment during breastfeeding [105]. Data from some HIV patients identified that the dose of tenofovir taken via breastfeeding by an infant of 3 kg weight is just 0.03% of the dose used in preventing of HIV transmission in infants [105–107]. Similar studies indicate that the exposure to lamivudine or tenofovir is lower from breastfeeding than from in utero exposure [107]. Thus, these data do not support the contraindication to use antiviral agents during breastfeeding. Further clinical studies are required to evaluate the safety of breastfeeding in mothers on antiviral therapy.

The end point of antiviral therapy aimed to reduce the risk of MTCT is typically in the immediate postpartum period, usually around 4 weeks after delivery, for mothers who meet the criteria for withdrawal of anti-viral drugs and plan to breastfeed their infants [108].

5. Conclusion

HBV infection in pregnancy is not only a unique challenge but also an important opportunity to prevent MTCT of HBV. Since conducting of double-blinded, randomized trails is not feasible in reality in pregnant women for ethical and other reasons, most of our data were obtained from open-labeled and non-randomized retrospective or prospective studies. Fortunately, lots of studies have reached relative consensuses and there are several procedures that are generally accepted to be feasible (shown in Fig. 1). Standard passive–active immunoprophylaxis with HBIG plus HBV vaccine in neonates within 12 h after delivery is proved to be successful in preventing approximately 90% of newborns from MTCT of HBV. For up to 9% of newborns suffered from MTCT of HBV after standard immunoprophylaxis, the main reason is perinatal transmission of HBV associated with high levels of viremia in mothers (serum HBV DNA $\geq 6 \log_{10}$ copies/ml or $5.3 \log_{10}$ IU/ml). Administration of antiviral agents such as tenofovir or telbivudine during pregnancy beginning at 28–32 weeks of gestation is reasonable in high viremic pregnancies. Based on standard passive–active immunoprophylaxis regimen, breastfeeding is recommended in HBsAg-positive mothers. There are still some controversial issues that need further concerns, including breastfeeding of infants by mothers on antiviral therapy, HBIG injection during pregnancy and the potential long-term side effect of antiviral agents to both HBV positive mothers and their infants.

Conflict of interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

[1] D. Lavanchy, Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures, J. Viral. Hepat. 11 (2004) 97–107.
[2] A. Goyal, J.M. Murray, The impact of vaccination and antiviral therapy on hepatitis B and hepatitis D epidemiology, PLoS One 9 (2014) e110143.
[3] D. Lavanchy, Worldwide epidemiology of HBV infection, disease burden, and vaccine prevention, J. Clin. Virol. Off. Publ. Pan Am. Soc. Clin. Virol. 34 (Suppl 1) (2005) S1–3.
[4] M.M. Jonas, Hepatitis B and pregnancy: an underestimated issue, Liver Int. Off. J. Int. Assoc. Study Liver 29 (Suppl 1) (2009) 133–139.
[5] C.J. Chen, U.H. Iloeje, H.I. Yang, Long-term outcomes in hepatitis B: the REVEAL-HBV study, Clin. Liver Dis. 11 (2007) 797–816, viii.
[6] I. Vodkin, H. Patton, Management of Hepatitis B virus infection during pregnancy, Minerva Gastroenterol. Dietol. 60 (2014) 205–214.
[7] L. Ma, N.R. Alla, X. Li, O.A. Mynbaev, Z. Shi, Mother-to-child transmission of HBV: review of current clinical management and prevention strategies, Rev. Med. Virol. 24 (2014) 396–406.
[8] G.R. Han, C.L. Xu, W. Zhao, Y.F. Yang, Management of chronic hepatitis B in pregnancy, World J. Gastroenterol. WJG 18 (2012) 4517–4521.
[9] K.W. Cheung, M.T. Seto, S.F. Wong, Towards complete eradication of hepatitis B infection from perinatal transmission: review of the mechanisms of in utero infection and the use of antiviral treatment during pregnancy, Eur. J. Obstet. Gynecol. Reprod. Biol. 169 (2013) 17–23.
[10] J. Hou, Z. Liu, F. Gu, Epidemiology and prevention of hepatitis B virus infection, Int. J. Med. Sci. 2 (2005) 50–57.
[11] B. Navabakhsh, N. Mehrabi, A. Estakhri, M. Mohamadnejad, H. Poustchi, Hepatitis B virus infection during pregnancy: transmission and prevention, Middle East J. Digest. Dis. 3 (2011) 92–102.
[12] A. Goudeau, B. Yvonnet, G. Lesage, F. Barin, F. Denis, P. Coursaget, et al., Lack of anti-HBc IgM in neonates with HBsAg carrier mothers argues against transplacental transmission of hepatitis B virus infection, Lancet 2 (1983) 1103–1104.
[13] K.H. Chau, M.P. Hargie, R.H. Decker, I.K. Mushahwar, L.R. Overby, Serodiagnosis of recent hepatitis B infection by IgM class anti-HBc, Hepatology 3 (1983) 142–149.

[14] R.P. Beasley, L.Y. Hwang, G.C. Lee, C.C. Lan, C.H. Roan, F.Y. Huang, et al., Prevention of perinatally transmitted hepatitis B virus infections with hepatitis B immune globulin and hepatitis B vaccine, Lancet 2 (1983) 1099–1102.
[15] D.Z. Xu, Y.P. Yan, B.C. Choi, J.Q. Xu, K. Men, J.X. Zhang, et al., Risk factors and mechanism of transplacental transmission of hepatitis B virus: a case-control study, J. Med. Virol. 67 (2002) 20–26.
[16] X.M. Li, Y.B. Yang, H.Y. Hou, Z.J. Shi, H.M. Shen, B.Q. Teng, et al., Interruption of HBV intrauterine transmission: a clinical study, World J. Gastroenterol. WJG 9 (2003) 1501–1503.
[17] M. Vermeulen, C. Coleman, J. Mitchel, R. Reddy, H. van Drimmelen, T. Ficket, et al., Sensitivity of individual-donation and minipool nucleic acid amplification test options in detecting window period and occult hepatitis B virus infections, Transfusion (Paris) 53 (2013) 2459–2466.
[18] Z. Zhang, A. Li, X. Xiao, Risk factors for intrauterine infection with hepatitis B virus, Int. J. Gynaecol. Obstetr. Off. Organ Int. Fed. Gynaecol. Obstetr. 125 (2014) 158–161.
[19] H. Zhang, C.Q. Pan, Q. Pang, R. Tian, M. Yan, X. Liu, Telbivudine or lamivudine use in late pregnancy safely reduces perinatal transmission of hepatitis B virus in real-life practice, Hepatology 60 (2014) 468–476.
[20] Y.Y. Xu, H.H. Liu, Y.W. Zhong, C. Liu, Y. Wang, L.L. Jia, et al., Peripheral blood mononuclear cell traffic plays a crucial role in mother-to-infant transmission of hepatitis B virus, Int. J. Biol. Sci. 11 (2015) 266–273.
[21] H. Bai, L. Zhang, L. Ma, X.G. Dou, G.H. Feng, G.Z. Zhao, Relationship of hepatitis B virus infection of placental barrier and hepatitis B virus intra-uterine transmission mechanism, World J. Gastroenterol. WJG 13 (2007) 3625–3630.
[22] C.V. Towers, T. Asrat, P. Rumney, The presence of hepatitis B surface antigen and deoxyribonucleic acid in amniotic fluid and cord blood, Am. J. Obstet. Gynecol. 184 (2001) 1514–1518, discussion 18–20.
[23] S.H. Han, Extrahepatic manifestations of chronic hepatitis B, Clin. Liver Dis. 8 (2004) 403–418.
[24] M. Yu, Q. Jiang, X. Gu, L. Ju, Y. Ji, K. Wu, et al., Correlation between vertical transmission of hepatitis B virus and the expression of HBsAg in ovarian follicles and placenta, PLoS One 8 (2013) e54246.
[25] M. Petrova, V. Kamburov, Breastfeeding and chronic HBV infection: clinical and social implications, World J. Gastroenterol. WJG 16 (2010) 5042–5046.
[26] N. Lv, X.D. Chu, Y.H. Sun, S.Y. Zhao, P.L. Li, X. Chen, Analysis on the outcomes of hepatitis B virus perinatal vertical transmission: nested case-control study, Eur. J. Gastroenterol. Hepatol. 26 (2014) 1286–1291.
[27] Z. Zhang, C. Chen, Z. Li, Y.H. Wu, X.M. Xiao, Individualized management of pregnant women with high hepatitis B virus DNA levels, World J. Gastroenterol. WJG 20 (2014) 12056–12061.
[28] E. Wiseman, M.A. Fraser, S. Holden, A. Glass, B.L. Kidson, L.G. Heron, et al., Perinatal transmission of hepatitis B virus: an Australian experience, Med. J. Aust. 190 (2009) 489–492.
[29] H. Zou, Y. Chen, Z. Duan, H. Zhang, C. Pan, Virologic factors associated with failure to passive–active immunoprophylaxis in infants born to HBsAg-positive mothers, J. Viral. Hepat. 19 (2012) e18–25.
[30] N.P. Nelson, D.J. Jamieson, T.V. Murphy, Prevention of perinatal hepatitis B virus transmission, J. Pediatr. Infect. Dis. Soc. 3 (2014) S7–S12.
[31] C.Q. Pan, Z.P. Duan, K.R. Bhamidimarri, H.B. Zou, X.F. Liang, J. Li, et al., An algorithm for risk assessment and intervention of mother to child transmission of hepatitis B virus, Clin. Gastroenterol. Hepatol. Off. Clin. Pract. J. Am. Gastroenterol. Assoc. 10 (2012) 452–459.
[32] G. Borgia, M.A. Carleo, G.B. Gaeta, I. Gentile, Hepatitis B in pregnancy, World J. Gastroenterol. WJG 18 (2012) 4677–4683.
[33] Z. Li, X. Hou, G. Cao, Is mother-to-infant transmission the most important factor for persistent HBV infection? Emerg. Microbes Infect. 4 (2015) e30.
[34] A.R. Zanetti, P. Ferroni, E.M. Magliano, P. Pirovano, C. Lavarini, A.L. Massaro, et al., Perinatal transmission of the hepatitis B virus and of the HBV-associated delta agent from mothers to offspring in northern Italy, J. Med. Virol. 9 (1982) 139–148.
[35] S. Terazawa, M. Kojima, T. Yamanaka, S. Yotsumoto, H. Okamoto, F. Tsuda, et al., Hepatitis B virus mutants with precore-region defects in two babies with fulminant hepatitis and their mothers positive for antibody to hepatitis B e antigen, Pediatr. Res. 29 (1991) 5–9.
[36] A. Bahn, K. Hilbert, U. Martine, J. Westedt, F. von Weizsacker, S. Wirth, Selection of a precore mutant after vertical transmission of different hepatitis B virus variants is correlated with fulminant hepatitis in infants, J. Med. Virol. 47 (1995) 336–341.
[37] M. Friedt, P. Gerner, E. Lausch, H. Trubel, B. Zabel, S. Wirth, Mutations in the basic core promotor and the precore region of hepatitis B virus and their selection in children with fulminant and chronic hepatitis B, Hepatology 29 (1999) 1252–1258.
[38] I. Cacciola, G. Cerenzia, T. Pollicino, G. Squadrito, S. Castellaneta, A.R. Zanetti, et al., Genomic heterogeneity of hepatitis B virus (HBV) and outcome of perinatal HBV infection, J. Hepatol. 36 (2002) 426–432.
[39] H. Komatsu, Hepatitis B virus: where do we stand and what is the next step for eradication? World J. Gastroenterol. WJG 20 (2014) 8998–9016.
[40] V.C. Wong, H.M. Ip, H.W. Reesink, P.N. Lelie, E.E. Reerink-Brongers, C.Y. Yeung, et al., Prevention of the HBsAg carrier state in newborn infants of mothers who are chronic carriers of HBsAg and HBeAg by administration of hepatitis-B vaccine and hepatitis-B immunoglobulin. Double-blind randomised placebo-controlled study, Lancet 1 (1984) 921–926.
[41] C. Lee, Y. Gong, J. Brok, E.H. Boxall, C. Gluud, Effect of hepatitis B immunisation in newborn infants of mothers positive for hepatitis B surface antigen: systematic review and meta-analysis, BMJ 332 (2006) 328–336.
[42] T. Piratvisuth, Optimal management of HBV infection during pregnancy, Liver Int. Off. J. Int. Assoc. Study Liver 33 (Suppl 1) (2013) 188–194.
[43] L. Zhang, X.E. Gui, C. Teter, H. Zhong, Z. Pang, L. Ding, et al., Effects of hepatitis B immunization on prevention of mother-to-infant transmission of hepatitis B virus and on the immune response of infants towards hepatitis B vaccine, Vaccine 32 (2014) 6091–6097.
[44] WHO, Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection, WHO Guidelines Approved by the Guidelines Review Committee, Geneva, 2015.
[45] T.T. Tran, Management of hepatitis B in pregnancy: weighing the options, Cleve. Clin. J. Med. 76 (Suppl 3) (2009) S25–9.
[46] A. Kumar, Hepatitis B virus infection and pregnancy: a practical approach, Indian J. Gastroenterol. Off. J. Indian Soc. Gastroenterol. 31 (2012) 43–54.
[47] M. Machaira, V. Papaevangelou, E.K. Vouloumanou, G.S. Tansarli, M.E. Falagas, Hepatitis B vaccine alone or with hepatitis B immunoglobulin in neonates of HBsAg+/HBeAg- mothers: a systematic review and meta-analysis, J. Antimicrob. Chemother. 70 (2015) 396–404.
[48] K.J. Lo, Y.T. Tsai, S.D. Lee, T.C. Wu, J.Y. Wang, G.H. Chen, et al., Immunoprophylaxis of infection with hepatitis B virus in infants born to hepatitis B surface antigen-positive carrier mothers, J. Infect. Dis. 152 (1985) 817–822.
[49] A. Milne, D.J. West, D.V. Chinh, C.D. Moyes, G. Poerschke, Field evaluation of the efficacy and immunogenicity of recombinant hepatitis B vaccine without HBIG in newborn Vietnamese infants, J. Med. Virol. 67 (2002) 327–333.
[50] M. Gambarin-Gelwan, Hepatitis B in pregnancy, Clin. Liver Dis. 11 (2007) 945–963, x.
[51] C. Buchanan, T.T. Tran, Management of chronic hepatitis B in pregnancy, Clin. Liver Dis. 14 (2010) 495–504.
[52] Z.J. Shao, L. Zhang, J.Q. Xu, D.Z. Xu, K. Men, J.X. Zhang, et al., Mother-to-infant transmission of hepatitis B virus: a Chinese experience, J. Med. Virol. 83 (2011) 791–795.
[53] F. Wong, R. Pai, J. Van Schalkwyk, E.M. Yoshida, Hepatitis B in pregnancy: a concise review of neonatal vertical transmission and antiviral prophylaxis, Ann. Hepatol. 13 (2014) 187–195.
[54] M.H. Chang, Cancer prevention by vaccination against hepatitis B, Recent Results Cancer Res. Fortschritte der Krebsforschung Progres dans les recherches sur le cancer 181 (2009) 85–94.
[55] M.H. Chang, Breakthrough HBV infection in vaccinated children in Taiwan: surveillance for HBV mutants, Antivir. Ther. 15 (2010) 463–469.
[56] J.S. Wang, Q.R. Zhu, Infection of the fetus with hepatitis B e antigen via the placenta, Lancet 355 (2000) 989.
[57] Q. Zhu, Q. Lu, S. Xiong, H. Yu, S. Duan, Hepatitis B virus S gene mutants in infants infected despite immunoprophylaxis, Chin. Med. J. 114 (2001) 352–354.
[58] B. Yucesoy, V.J. Johnson, K. Fluharty, M.L. Kashon, J.E. Slaven, N.W. Wilson, et al., Influence of cytokine gene variations on immunization to childhood vaccines, Vaccine 27 (2009) 6991–6997.
[59] L. Koumbi, A. Bertoletti, V. Anastasiadou, M. Machaira, W. Goh, N.G. Papadopoulos, et al., Hepatitis B-specific T helper cell responses in uninfected infants born to HBsAg+/HBeAg- mothers, Cell. Mol. Immunol. 7 (2010) 454–458.
[60] J.Y. Weissman, M.M. Tsuchiyose, M.J. Tong, R. Co, K. Chin, R.B. Ettenger, Lack of response to recombinant hepatitis B vaccine in nonresponders to the plasma vaccine, JAMA 260 (1988) 1734–1738.
[61] M.D. Young, D.L. Schneider, A.J. Zuckerman, W. Du, B. Dickson, W.C. Maddrey, Adult hepatitis B vaccination using a novel triple antigen recombinant vaccine, Hepatology 34 (2001) 372–376.
[62] R.P. Beasley, L.Y. Hwang, C.C. Lin, C.E. Stevens, K.Y. Wang, T.S. Sun, et al., Hepatitis B immune globulin (HBIG) efficacy in the interruption of perinatal transmission of hepatitis B virus carrier state. Initial report of a randomised double-blind placebo-controlled trial, Lancet 2 (1981) 388–393.
[63] R.P. Beasley, L.Y. Hwang, C.E. Stevens, C.C. Lin, F.J. Hsieh, K.Y. Wang, et al., Efficacy of hepatitis B immune globulin for prevention of perinatal transmission of the hepatitis B virus carrier state: final report of a randomized double-blind, placebo-controlled trial, Hepatology 3 (1983) 135–141.
[64] W.M. Xu, Y.T. Cui, L. Wang, H. Yang, Z.Q. Liang, X.M. Li, et al., Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multicentre, randomized, double-blind, placebo-controlled study, J. Viral. Hepat. 16 (2009) 94–103.
[65] A.E. Singh, S.S. Plitt, C. Osiowy, K. Surynicz, E. Kouadjo, J. Preiksaitis, et al., Factors associated with vaccine failure and vertical transmission of hepatitis B among a cohort of Canadian mothers and infants, J. Viral. Hepat. 18 (2011) 468–473.
[66] M. Yu, Q. Jiang, Y. Ji, H. Jiang, K. Wu, L. Ju, et al., The efficacy and safety of antiviral therapy with lamivudine to stop the vertical transmission of hepatitis B virus, Eur. J. Clin. Microbiol. Infect. Dis. Off. Publ. Eur. Soc. Clin. Microbiol. 31 (2012) 2211–2218.
[67] A. Ayres, L. Yuen, K.M. Jackson, S. Manoharan, A. Glass, M. Maley, et al., Short duration of lamivudine for the prevention of hepatitis B virus transmission in pregnancy: lack of potency and selection of resistance mutations, J. Viral. Hepat. 21 (2014) 809–817.

[68] C.L. Lai, E. Gane, Y.F. Liaw, C.W. Hsu, S. Thongsawat, Y. Wang, et al., Telbivudine versus lamivudine in patients with chronic hepatitis B, N. Eng. J. Med. 357 (2007) 2576–2588.
[69] Y.F. Liaw, E. Gane, N. Leung, S. Zeuzem, Y. Wang, C.L. Lai, et al., 2-year GLOBE trial results: telbivudine Is superior to lamivudine in patients with chronic hepatitis B, Gastroenterology 136 (2009) 486–495.
[70] L.J. Zhang, L. Wang, Blocking intrauterine infection by telbivudine in pregnant chronic hepatitis B patients, Zhonghua gan zang bing za zhi = Zhonghua ganzangbing zazhi = Chin. J. Hepatol. 17 (2009) 561–563.
[71] G.R. Han, M.K. Cao, W. Zhao, H.X. Jiang, C.M. Wang, S.F. Bai, et al., A prospective and open-label study for the efficacy and safety of telbivudine in pregnancy for the prevention of perinatal transmission of hepatitis B virus infection, J. Hepatol. 55 (2011) 1215–1221.
[72] M. Deng, X. Zhou, S. Gao, S.G. Yang, B. Wang, H.Z. Chen, et al., The effects of telbivudine in late pregnancy to prevent intrauterine transmission of the hepatitis B virus: a systematic review and meta-analysis, Virol. J. 9 (2012) 185.
[73] Y. Zhou, J. Zheng, H. Pan, C. Lu, [Long-term efficacy and safety of telbivudine in the treatment of childbearing patients with chronic hepatitis B], Zhonghua gan zang bing za zhi = Zhonghua ganzangbing zazhi = Chin. J. Hepatol. 22 (2014) 573–576.
[74] Q. Wu, H. Huang, X. Sun, M. Pan, Y. He, S. Tan, et al., Telbivudine prevents vertical transmission of hepatitis B virus from women with high viral loads: a prospective long-term study, Clin. Gastroenterol. Hepatol. Off. Clin. Pract. J. Am. Gastroenterol. Assoc. 13 (2015) 1170–1176.
[75] M. Giles, K. Visvanathan, J. Sasadeusz, Antiviral therapy for hepatitis B infection during pregnancy and breastfeeding, Antivir. Ther. 16 (2011) 621–628.
[76] C.Q. Pan, L.J. Mi, C. Bunchorntavakul, J. Karsdon, W.M. Huang, G. Singhvi, et al., Tenofovir disoproxil fumarate for prevention of vertical transmission of hepatitis B virus infection by highly viremic pregnant women: a case series, Dig. Dis. Sci. 57 (2012) 2423–2429.
[77] M.K. Celen, D. Mert, M. Ay, T. Dal, S. Kaya, N. Yildirim, et al., Efficacy and safety of tenofovir disoproxil fumarate in pregnancy for the prevention of vertical transmission of HBV infection, World J. Gastroenterol. WJG 19 (2013) 9377–9382.
[78] A.J. Greenup, P.K. Tan, V. Nguyen, A. Glass, S. Davison, U. Chatterjee, et al., Efficacy and safety of tenofovir disoproxil fumarate in pregnancy to prevent perinatal transmission of hepatitis B virus, J. Hepatol. 61 (2014) 502–507.
[79] H.L. Chen, C.N. Lee, C.H. Chang, Y.H. Ni, M.K. Shyu, S.M. Chen, et al., Efficacy of maternal tenofovir disoproxil fumarate in interrupting mother-to-infant transmission of hepatitis B virus, Hepatology 62 (2015) 375–386.
[80] R.S. Brown Jr., E.C. Verna, M.R. Pereira, H.H. Tilson, C. Aguilar, C.S. Leu, et al., Hepatitis B virus and human immunodeficiency virus drugs in pregnancy: findings from the Antiretroviral Pregnancy Registry, J. Hepatol. 57 (2012) 953–959.
[81] G. Dusheiko, Interruption of mother-to-infant transmission of hepatitis B: time to include selective antiviral prophylaxis, Lancet 379 (2012) 2019–2021.
[82] S. Degli Esposti, D. Shah, Hepatitis B in pregnancy: challenges and treatment, Gastroenterol. Clin. North Am. 40 (2011) 355–372, viii.
[83] J.C. Dunkelberg, E.M. Berkley, K.W. Thiel, K.K. Leslie, Hepatitis B and C in pregnancy: a review and recommendations for care, J. Perinatol. Off. J. California Perinatal Assoc. 34 (2014) 882–891.
[84] N.H. Bzowej, Optimal management of the hepatitis B patient who desires pregnancy or is pregnant, Curr. Hepatitis Rep. 11 (2012) 82–89.
[85] J. Petersen, HBV treatment and pregnancy, J. Hepatol. 55 (2011) 1171–1173.
[86] Q. Zhu, Q. Lu, X. Gu, H. Xu, S. Duan, A preliminary study on interruption of HBV transmission in uterus, Chin. Med. J. 110 (1997) 145–147.
[87] Z. Shi, X. Li, L. Ma, Y. Yang, Hepatitis B immunoglobulin injection in pregnancy to interrupt hepatitis B virus mother-to-child transmission-a meta-analysis, Int. J. Infect. Dis. IJID: Off. Publ. Int. Soc. Infect. Dis. 14 (2010) e622–34.
[88] H. Xu, T. Zeng, J.Y. Liu, Y. Lei, S. Zhong, Y.J. Sheng, et al., Measures to reduce mother-to-child transmission of Hepatitis B virus in China: a meta-analysis, Dig. Dis. Sci. 59 (2014) 242–258.
[89] H. Jin, Y. Zhao, Z. Tan, X. Zhang, B. Wang, P. Liu, Immunization interventions to interrupt hepatitis B virus mother-to-child transmission: a meta-analysis of randomized controlled trials, BMC Pediatr. 14 (2014) 307.
[90] Z.H. Han, L.H. Zhong, J. Wang, Q.L. Zhao, Y.G. Sun, L.W. Li, et al., The impact of antepartum injection of hepatitis B immunoglobulin on maternal serum HBV DNA and anti-HBs in the newborns, Zhonghua nei ke za zhi. 46 (2007) 376–378.
[91] X.M. Xiao, A.Z. Li, X. Chen, Y.K. Zhu, J. Miao, Prevention of vertical hepatitis B transmission by hepatitis B immunoglobulin in the third trimester of pregnancy, Int. J. Gynaecol. Obstetr. Off. Organ Int. Fed. Gynaecol. Obstetr. 96 (2007) 167–170.
[92] J. Yuan, J. Lin, A. Xu, H. Li, B. Hu, J. Chen, et al., Antepartum immunoprophylaxis of three doses of hepatitis B immunoglobulin is not effective: a single-centre randomized study, J. Viral. Hepat. 13 (2006) 597–604.
[93] C.P. Liu, Y.L. Zeng, M. Zhou, L.L. Chen, R. Hu, L. Wang, et al., Factors associated with mother-to-child transmission of hepatitis B virus despite immunoprophylaxis, Int. Med. 54 (2015) 711–716.
[94] Z. Guo, X.H. Shi, Y.L. Feng, B. Wang, L.P. Feng, S.P. Wang, et al., Risk factors of HBV intrauterine transmission among HBsAg-positive pregnant women, J. Viral. Hepat. 20 (2013) 317–321.
[95] W.H. Chen, C.S. Yin, Y.K. Chang, J.S. Yan, M.L. Chu, Neonatal gastric aspirates as a predictor of perinatal hepatitis B virus infections, Int. J. Gynaecol. Obstetr. Off. Organ Int. Fed. Gynaecol. Obstetr. 60 (1998) 15–21.
[96] J.B. Hill, J.S. Sheffield, M.J. Kim, J.M. Alexander, B. Sercely, G.D. Wendel, Risk of hepatitis B transmission in breast-fed infants of chronic hepatitis B carriers, Obstet. Gynecol. 99 (2002) 1049–1052.
[97] X. Chen, J. Chen, J. Wen, C. Xu, S. Zhang, Y.H. Zhou, et al., Breastfeeding is not a risk factor for mother-to-child transmission of hepatitis B virus, PLoS One 8 (2013) e55303.
[98] Y. Zheng, Y. Lu, Q. Ye, Y. Xia, Y. Zhou, Q. Yao, et al., Should chronic hepatitis B mothers breastfeed? A meta analysis, BMC Public Health 11 (2011) 502.
[99] L. Zhang, X. Gui, J. Fan, B. Wang, H. Ji, R. Yisilafu, et al., Breast feeding and immunoprophylaxis efficacy of mother-to-child transmission of hepatitis B virus, J. Maternal-fetal Neonatal Med. Off. J. Eur. Assoc. Perinatal Med., Fed. Asia Oceania Perinatal Soc., Int. Soc. Perinatal Obstet. 27 (2014) 182–186.
[100] Z. Shi, Y. Yang, H. Wang, L. Ma, A. Schreiber, X. Li, et al., Breastfeeding of newborns by mothers carrying hepatitis B virus: a meta-analysis and systematic review, Arch. Pediatr. Adolesc. Med. 165 (2011) 837–846.
[101] A. Montoya-Ferrer, A.M. Zorrilla, J. Viljoen, J.P. Moles, M.L. Newell, P. Van de Perre, et al., High Level of HBV DNA Virus in the Breast Milk Seems not to Contraindicate Breastfeeding, Mediterranean J. Hematol. Infect. Dis. 7 (2015) e2015042.
[102] A.S. Lok, B.J. McMahon, Chronic hepatitis B: update 2009, Hepatology 50 (2009) 661–662.
[103] EASL clinical practice guidelines: management of chronic hepatitis B virus infection, J. Hepatol. 57 (2012) 167–185.
[104] J. Dionne-Odom, A.T. Tita, N.S. Silverman, #38: Hepatitis B in pregnancy screening, treatment, and prevention of vertical transmission, Am. J. Obstet. Gynecol. 214 (2016) 6–14.
[105] S. Benaboud, A. Pruvost, P.A. Coffie, D.K. Ekouevi, S. Urien, E. Arrive, et al., Concentrations of tenofovir and emtricitabine in breast milk of HIV-1-infected women in Abidjan, Cote d'Ivoire, in the ANRS 12109 TEmAA Study, Step 2, Antimicrob. Agents Chemother. 55 (2011) 1315–1317.
[106] L. Palombi, M.F. Pirillo, E. Marchei, H. Jere, J.B. Sagno, R. Luhanga, et al., Concentrations of tenofovir, lamivudine and efavirenz in mothers and children enrolled under the Option B-Plus approach in Malawi, J. Antimicrob. Chemother. (2015).
[107] S. Ehrhardt, C. Xie, N. Guo, K. Nelson, C.L. Thio, Breastfeeding while taking lamivudine or tenofovir disoproxil fumarate: a review of the evidence, Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 60 (2015) 275–278.
[108] H. Patton, T.T. Tran, Management of hepatitis B during pregnancy, Nat. Rev. Gastroenterol. Hepatol. 11 (2014) 402–409.