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**Novel insights in the prevention of perinatal transmission of hepatitis B**

Tziomalos K *et al*. Prevention of perinatal transmission of HBV

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**Abstract**

Perinatal transmission of hepatitis B virus (HBV) infection is major contributor to the growing burden of chronic hepatitis B worldwide. Administration of HBV immunoglobulin and HBV vaccination as soon after pregnancy as possible are the mainstay of prevention of perinatal transmission of HBV infection. In women with high viral loads, antiviral prophylaxis also appears to be useful. Lamivudine, telbivudine and tenofovir have been shown to be both safe and effective in this setting but tenofovir is the first-line option due to its low potential for resistance and more favorable safety profile.

**Key words:** Perinatal transmission; Hepatitis B; Lamivudine; Telbivudine; Tenofovir

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**Core tip:** Administration of hepatitis B virus (HBV) immunoglobulin and HBV vaccination as soon after pregnancy as possible are the mainstay of prevention of perinatal transmission of HBV infection. In women with high viral loads, antiviral prophylaxis with tenofovir also appears to be useful.

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**INTRODUCTION**

Perinatal transmission of hepatitis B virus (HBV) is a major healthcare problem, particularly in low-income countries with high prevalence of chronic hepatitis B (CHB)[1]. In regions where CHB is endemic, HBeAg(+) mothers transmit HBV in 70%-90% of their children if prophylaxis is not administered1]. In addition, high CHB prevalence, poor compliance with medical care and barriers to health care among low-income population groups, especially in immigrants and Roma population, are associated with increased perinatal HBV transmission even in developed European countries[2,3]. Women with high viral loads are at particularly increased risk to transmit hepatitis B to their offspring[4-7]. In many CHB endemic areas, perinatal transmission of hepatitis B is the major cause of transmission of hepatitis B[8,9]. Moreover, progression from HBV infection to CHB is substantially more frequent in the offspring of HBeAg(+) women than in patients who are exposed to HBV during adulthood[10,11]. Indeed, approximately 90% of the former will progress to CHB[10,11].

**ROLE OF HBV IMMUNOGLOBULIN AND HBV VACCINATION**

Administration of HBV immunoglobulin and HBV vaccination prevents most cases of perinatal HBV transmission[1]. Nevertheless, children born from women with high viral load are still at considerable risk for acquiring HBV despite the administration of HBV immunoglobulin and HBV vaccination [8%-18% when HBV deoxyribonucleic acid (DNA) levels are > 107-108 copies/mL][4,12-14]. On the other hand, a recent study reported that prompt administration of HBV immunoglobulin (*i.e.* within 4 h after birth) and/or an increase in the number of HBV vaccination doses (at birth and at 1, 2, 4 and 6 mo) resulted in very low rates of perinatal HBV transmission (2%) in HBeAg-positive women with HBV DNA levels > 200000 IU/mL[15].

**ROLE OF NUCLEOSIDE ANALOGUES**

Several studies also showed that nucleoside analogues combined with administration of HBV immunoglobulin and HBV vaccination are more effective in the prevention of perinatal HBV transmission than administration of HBV immunoglobulin and HBV vaccination alone[16]. In a meta-analysis of 5 small randomized controlled trials (RCTs, *n* = 444 pregnant women), treatment with lamivudine combined with administration of HBV immunoglobulin and HBV vaccination reduced infant HBsAg seropositivity by 11.7% and infant HBV DNA positivity by 21.2% compared with administration of HBV immunoglobulin and HBV vaccination[17]. In a meta-analysis of 4 small RCTs (*n* = 293 pregnant women), telbivudine also reduced infant HBsAg seropositivity by 15.8% and infant HBV DNA positivity by 16.2% compared to the control group[17]. Three early small nonrandomized studies (*n* = 307 pregnant women) showed that tenofovir also reduces the risk for perinatal HBV transmission[18-20]. In a more recent RCT in HBeAg-positive mothers with viral load > 200000 IU/mL (*n* = 200), HBV transmission was observed in 5% of cases who received tenofovir in addition to HBV immunoglobulin/HBV vaccination compared with 18% in mothers treated with HBV immunoglobulin/HBV vaccination alone[14]. In contrast, in a larger RCT (*n* = 331), tenofovir combined with HBV immunoglobulin/HBV vaccination did not reduce the risk of HBV transmission compared with HBV immunoglobulin/HBV vaccination alone[15]. However, rates of HBV transmission in the latter group were very low (2%) and it is possible that the study was not powered to show superiority of tenofovir[15].

Very few studies compared the efficacy of different nucleoside analogues in the prevention of perinatal HBV transmission. In two non-randomized studies (*n* = 690 pregnant women), lamivudine was equally effective with telbivudine[21,22] and in another non-randomized study (*n* = 120 pregnant women), lamivudine was similarly effective with tenofovir[18]. Lamivudine, telbivudine and tenofovir also appear to be safe during pregnancy and do not increase the risk of congenital malformation, prematurity or maternal complications[17,23]. However, it should be emphasized that tenofovir and telbivudine are both Food and Drug Administration (FDA) pregnancy category B drugs (*i.e.,* no risk in animal studies, unknown in humans) whereas lamivudine is FDA pregnancy category C drug (*i.e.,* teratogenic in animal studies, unknown in humans)[24]. It has also been shown that in the United States, a country with very low prevalence of CHB, combining a nucleoside analogue with HBV immunoglobulin/HBV vaccination is more cost-effective than HBV immunoglobulin/HBV vaccination alone[25]. Nevertheless, it should be emphasized that none of these agents are licensed for use during pregnancy.

Current guidelines recommend screening of all pregnant women for CHB during the first trimester of pregnancy[24,26,27]. In all pregnant women with HBV DNA levels > 200000 IU/mL and/or > 6-7 log10 IU/mL or HBsAg levels > 4 log10 IU/mL, antiviral prophylaxis with tenofovir should start at week 24-32 of gestation and continue for up to 4-12 wk after delivery[24,26,27]. Tenofovir is preferred over lamivudine and telbivudine because of lower resistance rates and because it is a FDA pregnancy category B drug[24,26,27].

**ROLE OF CAESAREAN SECTION**

The role of caesarean section in the prevention of perinatal transmission of HBV infection is unclear. In a recent meta-analysis of 10 studies (*n* = 5091 newborns), caesarean section reduced the incidence HBV transmission by 38% compared with vaginal delivery (95%CI: 0.40-0.98; *P* = 0.04)[28]. However, the benefit of caesarean section was smaller in studies where hepatitis B immunoglobulin was administered to all women[28]. Moreover, caesarean section did not reduce the risk of vertical HBV transmission in HBeAg(+) women[28]. Accordingly, current guidelines do not recommend caesarean section for the prevention of perinatal transmission of HBV infection due to insufficient data[26].

**BREASTFEEDING IN HBsAg(+) WOMEN**

Regarding breastfeeding, current guidelines state that it is not contraindicated in HBsAg(+) women who are not receiving nucleoside analogues, since breast milk contains the lowest concentrations of HBV among body fluids and breast feeding does not increase the risk of HBV transmission in women who receive HBV immunoglobulin and HBV vaccination[24,26,27,29]. Moreover, breastfeeding is also not prohibited in women who are receiving prophylaxis with tenofovir, since this agent is excreted in very small amounts in breast milk[24,26,27,30,31].

**CONCLUSION**

Perinatal transmission of HBV infection is major contributor to the growing burden of CHB worldwide. Administration of HBV immunoglobulin and HBV vaccination as soon after pregnancy as possible are the mainstay of prevention of perinatal transmission of HBV infection. In women with high viral loads, antiviral prophylaxis with tenofovir also appears to be useful. Strategies to improve the awareness of this major healthcare problem are also needed to curb the rising incidence of CHB infection.

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