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Original Article

Hepatitis B virus infection: Prevention of mother-to-child transmission and exacerbation during pregnancy☆

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ABSTRACT

The aims of this study were to assess the effect of maternal screening for hepatitis B (HB) virus and a perinatal prevention program of mother-to-child transmission, and to identify clinical characteristics and findings associated with HB exacerbation during pregnancy. This prospective cohort study enrolled 3796 pregnant women and their neonates with informed consent. Pregnant women underwent maternal universal screening for HBs antigen (Ag) in the first trimester. If HBs Ag was positive, serum levels of HBe Ag, alanine transaminase (AST), aspartate aminotransferase (ALT), and HB virus (HBV) DNA were measured. All neonates delivered from HBs Ag-positive women were given HB immune globulin and HB vaccine based on the guidelines of the perinatal prevention program. Of the 3796 pregnant women, 40 (1.05%) tested positive for HBs Ag. Three (7.5%) of the 40 HBs Ag-positive women experienced exacerbation of HBV infection during pregnancy. Serum levels of AST (median 776 vs. 22 mIU/ml, $p < 0.01$), ALT (median 325 vs. 15 mIU/ml, $p < 0.01$), and HBV-DNA (median 9.1 vs. 5.4 log copies/ml, $p < 0.05$), and frequencies of HBe Ag-positive (100% vs. 29.7%, $p < 0.05$) and symptoms of itching or general fatigue (66.7% vs. 0%, $p < 0.01$) in three women with exacerbation of HBV infection were significantly higher than those in 37 women without exacerbation. There was no case of mother-to-child transmission, suggesting the perinatal HBV prevention program was effective. Levels of HBe Ag, liver enzymes, and HBV-DNA as well as symptoms of itching and general fatigue should be carefully monitored for HBs Ag-positive women during pregnancy and the postpartum period.

1. Introduction

Chronic hepatitis B (HB) virus infection is an important global health problem. The World Health Organization (WHO) estimates that approximately 400 million people worldwide are chronically infected with HB virus (HBV) [1,2]. There are regional differences in HBV epidemics. In sub-Saharan Africa, the Pacific, and particularly Asia, HBV infection is highly endemic, while western and northern European countries and North America are not in the endemic areas [2]. About 15%–40% of infected patients will suffer from serious complications, such as cirrhosis and hepatocellular carcinoma [1–3]. Most of them are infected during the perinatal period or in early childhood [1]. The mother-to-child transmission rate in cases with positive HB envelop (HBe) antigen (Ag) is almost 100% and that about 90% of them become HB surface (HBs) Ag carriers if they are not prophylactically treated [4]. Immunoprophylaxis of newborns consistently reduces the rate to 10% [1,5]. For this reason, it is important for HBs Ag positive mothers to have immunoprophylaxis for their infants. In Japan, maternal screening for HBV and a perinatal HBV prevention program was started in 1986.

Helper T (Th) cells are part of the immune system. During pregnancy, Th-1 cells are suppressed, but Th-2 cells are enhanced. This change in the immune system may cause a flare-up of chronic HBV infection [6]. Exacerbation of HBV infection usually resolves without treatment, but some cases may be severe, resulting in liver failure [7,8]. Exacerbation of HBV infection during pregnancy was

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observed in 6% of women with chronic HBV infection [3]. Most clinical studies have emerged from HBV endemic areas. There are few reports about exacerbation of HBV infection in HBV non-endemic area, such as Japan.

The aim of this study was to assess the effect of maternal universal screening for HBV and a perinatal prevention program of mother-to-child transmission. This study also aimed to determine the frequency of exacerbation of HBV infection during pregnancy, and to identify clinical characteristics and findings associated with exacerbation.

2. Material and methods

2.1. The effectiveness of maternal screening for HBV and perinatal HBV prevention program

The institutional ethical boards of the Kobe University Hospital approved this prospective cohort study. Between July 2008 and December 2016, 3796 pregnant women and their neonates delivered at the university hospital and were enrolled.

All pregnant women underwent maternal universal screening for HBV using HBs Ag test in the first trimester. If HBs Ag was positive, serum levels of HB envelop (HBe) Ag, liver enzymes including alanine transaminase (ALT; normal 7–23 mIU/ml), aspartate aminotransferase (AST; normal 13–30 mIU/ml), and HBV-DNA titers (real-time PCR assay, COBAS® TaqMan® HBV Test, v2.0, F. Hoffmann-La Roche Ltd, Basel, Switzerland; normal <2.1 log copies/ml) were periodically measured throughout pregnancy. All infants born to HBs Ag positive-mothers received HB immune globulin (HBIG; 200 units, DRIED HB GLOBULIN for I.M. injection 200 units 「NICHIYAKU」, NIHON PHARMACEUTICAL CO., LTD, Tokyo, Japan) and HB vaccine (0.5 ml, Bimmugen, KM Biologics Co., LTD, Kumamoto, Japan; 0.5 ml, HEPTAVAX-II Aqueous Suspension for Injection Syringes 0.5 mL, MSD K.K. a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA) based on the guidelines of a perinatal HBV prevention program in Japan (Fig. 1). Until September 2013, all newborns from HBs Ag-positive mothers received HBIG within 12 h and at 2 months after birth, and received HB vaccine at one, two, and five months after birth. After October 2013, all newborns from HBs Ag-positive mothers received HBIG within 12 h after birth, and received HB vaccine within 12 h, and at one and six months after birth. HBs Ag tests and HBs antibody (Ab) measurements were performed at 6–12 months after birth for all infants who received prophylaxis with HBIG and HB vaccine.

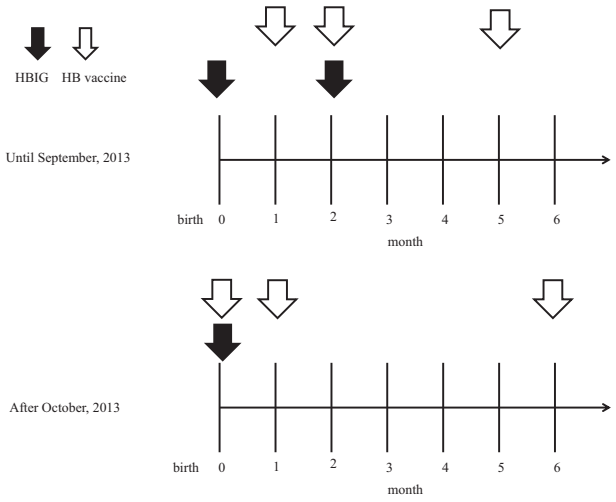

Fig. 1. Prevention program of mother-to-child transmission of hepatitis B virus in Japan. Black arrow indicates HBIG. White arrow indicates HB vaccine. HB, hepatitis B; HBIG, HB immunoglobulin.

Prophylaxis failure was defined as a HBs Ag-positive in the infants at 6–12 months after birth. If HBs Ab titers in the infant at 6–12 months after birth were <10 mIU/ml, the same type of HB vaccine (Bimmugen) or other type of HB vaccine (HEPTAVAX-II Aqueous Suspension for Injection Syringes 0.5 mL) was re-administered. If the infant who received administration of HBIG and HB vaccine had negative results for HBs Ag, and serum levels of HBs Ab were ≥10 mIU/ml at 6–12 months after birth, the perinatal HBV prevention program was considered effective.

2.2. Prevalence and clinical features of HB exacerbation during pregnancy

A total of 40 (1.05%) of the 3796 pregnant women tested positive for HBs Ag. Exacerbation of HBV infection during pregnancy was defined as an elevation of serum ALT levels to 5 or more times the upper normal limit of ALT [3,7,9]. The serum baseline levels of HBs Ag, HBe Ag, HBV-DNA, AST, and ALT were defined as those at 1 year before current conception, or those in the first trimester, if laboratory data prior to pregnancy were not available [3].

Clinical characteristics and blood test results were compared between women with and without exacerbation of HBV infection during pregnancy. Differences between the two groups were analyzed using the Mann–Whitney *U* test, and Fisher's exact test. *P* values < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS software, version 19 (SPSS Inc., Chicago, IL, USA).

3. Results

Fig. 2 shows a flow-chart of maternal screening and a prevention program of mother-to-child transmission of HBV. All 40 neonates from HBs Ag-positive pregnant women received prophylaxis with HBIG and HB vaccine based on the HBV prevention program in Japan. Five infants moved and were not followed up. Thirty-five of the 40 infants underwent testing for HBs Ag and HBs Ab at 6–12 months of age, and all 35 infants tested negative for HBs Ag. Thirty-three (94.3%) of the 35 infants had the serum HBs Ab levels of ≥10 mIU/ml, and the remaining two (5.7%) had those of <10 mIU/ml. The two infants with HBs Ab <10 mIU/ml again received the same type of HB vaccine, and acquired immunity against HBV.

Table 1 shows clinical characteristics and laboratory findings of 40 pregnant women with a positive test for HBs Ag. Three (7.5%) of the 40 HBs Ag-positive pregnant women experienced exacerbation of HBV infection during pregnancy. Maximum serum levels of AST (median 776 vs. 22 mIU/ml, $p < 0.01$), ALT (median 325 vs. 15 mIU/ml, $p < 0.01$), and HBV-DNA (median 9.1 vs. 5.4 log copies/ml, $p < 0.05$), frequencies of HBe Ag-positive (100% vs. 29.7%, $p < 0.05$) and symptoms of itching or general fatigue (66.7% vs. 0%, $p < 0.01$) in three women with exacerbation of HBV infection were significantly higher than those in 37 women without exacerbation.

Table 2 shows clinical characteristics and laboratory findings of 14 pregnant women with a positive test for HBe Ag. Three (21%) of the 14 HBe Ag-positive pregnant women experienced exacerbation of HBV infection during pregnancy. Maximum serum levels of AST (median 776 vs. 22 mIU/ml, $p < 0.01$), ALT (median 325 vs. 15 mIU/ml, $p < 0.01$) in three HBe Ag-positive women with exacerbation of HBV infection during pregnancy were significantly higher than those in 11 HBe Ag-positive women without exacerbation. Conversely, baseline serum levels of HBs antigen (median 3086 vs. 27,700, IU/ml, $p < 0.01$) in those with exacerbation were significantly lower than those without exacerbation.

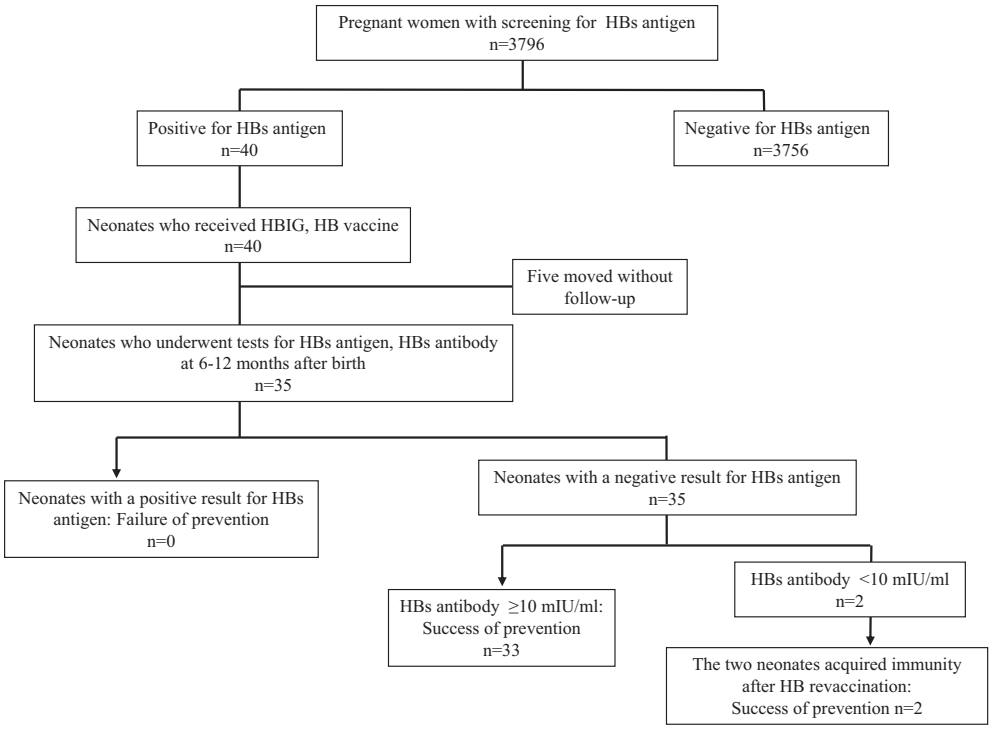

Fig. 2. A flow-chart of maternal screening and prevention program of mother-to-child transmission of hepatitis B virus. HB, hepatitis B; HBs, hepatitis B surface.

Table 1
Clinical characteristics and laboratory findings of 40 pregnant women with a positive test for HBs antigen.

Findings	All n = 40	Exacerbationn = 3	No exacerbationn = 37	*P*-Value
Age (year-old)	32 (23–44)	30 (28–33)	32 (23–44)	0.5
Gravidity	2 (1–6)	2 (1–6)	2 (1–6)	0.7
Parity	0 (0–3)	0 (0–1)	0 (0–3)	0.6
Gestational week at delivery	39 (25–41)	36 (35–39)	39 (25–41)	0.2
Baseline AST (mIU/ml)	17 (12–32)	22 (13–32)	17 (12–25)	0.5
Maximum AST (mIU/ml) during pregnancy	22 (13–829)	776 (338–829)	22 (13–56)	<0.01
Baseline ALT (mIU/ml)	13 (7–35)	21 (11–31)	13 (7–35)	0.2
Maximum ALT (mIU/ml) during pregnancy	17.5 (8–732)	325 (325–732)	15 (8–79)	<0.01
Baseline HBV-DNA (log copies/ml)	4.1 (1.8–9.4)	5.7 (3.4–6)	4.0 (1.8–9.4)	0.5
Maximum HBV-DNA (log copies/ml) during pregnancy	5.4 (2.0–10.1)	9.1 (9.1–10.1)	5.4 (2.0–9.7)	<0.05
Positive HBe antigen	35.0%	100.0%	29.7%	<0.05
Itching, general fatigue	5.0%	66.7%	0%	<0.01

Median (range)
AST, asparatate transaminase; ALT, alanine transaminase; HBV; hepatitis B virus; HBs, hepatitis B surface; HBe, Hepatitis B envelope.

Table 2
Clinical characteristics and laboratory findings of 14 pregnant women with a positive test for HBe antigen.

Findings	All n = 14	Exacerbationn = 3	No exacerbationn = 11	*P*-Value
Age (year-old)	30 (23–44)	30 (28–33)	30 (23–44)	0.9
Gravidity	2 (1–6)	2 (1–6)	2 (1–6)	0.6
Parity	0 (0–3)	0 (0–1)	0 (0–3)	0.6
Gestational week at delivery	38 (25–41)	36 (35–39)	38 (25–41)	0.5
Baseline AST (mIU/ml)	20 (12–32)	22 (13–32)	19 (12–24)	0.5
Maximum AST (mIU/ml) during pregnancy	23 (15–829)	776 (338–829)	22 (15–56)	<0.01
Baseline ALT (mIU/ml)	16 (9–35)	21 (11–31)	14 (9–35)	0.4
Maximum ALT (mIU/ml) during pregnancy	20 (8–732)	325 (325–732)	15 (8–79)	<0.01
Baseline HBV-DNA (log copies/ml)	8.2 (2.7–9.4)	5.7 (3.4–6)	9.0 (2.7–9.4)	0.1
Maximum HBV-DNA (log copies/ml) during pregnancy	9.1 (5.4–10.1)	9.1 (9.1–10.1)	9.1 (5.4–9.7)	0.3
Baseline HBs antigen (IU/ml)	18,737(1927–105411)	3086 (1927–3364)	27,700(3666–105411)	<0.01
Maximum HBs antigen (IU/ml) during pregnancy	34,443(2912–73436)	16,496 (3501–21251)	49,516(2912–73436)	0.1

Median (range)
AST, asparatate transaminase; ALT, alanine transaminase; HBV; hepatitis B virus; HBs, hepatitis B surface; HBe, Hepatitis B envelope.

Table 3 shows clinical characteristics and laboratory findings for three cases with exacerbation of HBV infection during pregnancy. In Case 1, serum baseline levels of HBe Ag (246 S/CO), ALT (31 mU/ml), and HBV-DNA level (3.4 log copies/ml) increased to 1500 S/CO, 732 mU/ml, and 9.1 log copies/ml at 36 gestational week (GW), respectively. In Case 2, serum baseline levels of HBe Ag (5.2 S/CO), ALT (11 mU/ml), and HBV-DNA level (5.7 log copies/ml) increased to 252 S/CO at 26 GW, 325 mU/ml at 28 GW, and 10.1 log copies/ml at 27 GW, respectively. In Case 3, serum baseline levels of HBe Ag (70 S/CO), ALT (21 mU/ml), and HBV-DNA level (6.0 log copies/ml) increased to 440 S/CO at 26 GW, 325 mU/ml, and 9.1 log copies/ml at 28 GW, respectively.

One of the three women received intravenous administration of ritodrine hydrochloride and magnesium sulfate during pregnancy due to threatened premature labor (Case 2), whereas the remaining two cases had neither liver-related nor other events during pregnancy. Two of the three women had clinical symptoms such as itching and general fatigue (Case 1 and Case 2). Although the three women had high serum levels of HBV-DNA, none received antivirus therapy during pregnancy. Case 1 experienced exacerbation of HBV infection at 36 GW, and received medication of fresh frozen plasma due to low levels of blood coagulation factors. After cesarean section was performed, HB exacerbation in Case 1 resolved spontaneously. HB exacerbation in Case 2 and Case 3 occurred during the second trimester, and resolved spontaneously. These two pregnancies ended in vaginal delivery. During the postpartum period, there was no exacerbation of HBV infection in the three cases.

4. Discussion

The WHO estimated the prevalence of HBs Ag in the Japanese population as 2%–4% in 2005 [10]. Ninety percent of infants born to HBe Ag-positive mothers become HBs Ag carriers if they didn't receive appropriate prophylaxis [4]. The present study demonstrated that a perinatal HBV prevention program between July 2008 and December 2016 was effective because there was no case of mother-to-child transmission, although the area and the period of participation were limited. The present also study found frequencies of exacerbation of HBV infection during pregnancy as 0.08% (3/3796 pregnant women), 7.5% (3/40 HBs Ag-positive women) and 21.4% (3/14 HBe Ag-positive women). Maximum blood AST, ALT and HBV-DNA levels, frequencies of HBe Ag-positive and symptoms of itching or general fatigue in women with exacerbation of HBV infection during pregnancy were significantly higher than those in women without exacerbation.

The prevalence of HBs Ag-positive pregnant women varies widely depending on the region. In countries, where the prevalence of HBs Ag exceeds 8%, perinatal transmission accounts for only 10%–20% of persistent HBV infections in infants. In contrast, the major route of infection among young children is not horizontal infection but perinatal infection in countries where the prevalence of HBs Ag is <1.0% including Japan [11,12]. Therefore, it is very important to implement maternal screening for HBV and a prevention program of mother-to-child transmission to reduce the population of HBV carriers. In Japan, everyone receives low-cost medical care through the national health insurance system [13]. Additionally, pregnant women are entitled to receive pregnancy health checkups and a Maternal and Child Health handbook following registration at a local municipal office. To prevent perinatal HBV transmission among infants born to HBs Ag-positive mothers, maternal screening for HB Ag and a perinatal HBV prevention program are strongly recommended in Japan [14].

In the present study, there were three cases with exacerbation of HBV infection during pregnancy. Two of the three women had

Table 3
Clinical characteristics and laboratory findings of three cases with exacerbation of hepatitis B virus infection during pregnancy.

Case No.	Age (year- old)	Gravidity/Parity	GW at delivery	Mode of delivery	Sex	Birth weight (g)	Obstetricalcomplications	Medication during pregnancy	Clinical symptom [GW]	HBs antigen (IU/ml)	HBeantigen (S/CO)	HBV-DNA (log copies/ml)	AST (mIU/ml)	ALT (mIU/ml)
										Baseline/ Max. during preg. [GW]	Baseline/ Max. during preg. [GW]	Baseline/Max. during preg. [GW]	Baseline/Max. during preg. [GW]	Baseline/Max. during preg. [GW]
1	30	2/1	36	CS	female	2950	Gestational diabetes mellitus	None	Itching [36], general fatigue [36]	1927/3501 [36]	246/1500 [36]	3.4/9.1 [36]	32/776 [36]	31/732 [36]
2	33	6/2	35	VD	male	2654	Threatened premature labor, recurrent miscarriage	MgSO4, ritodrine hydrochloride	Itching [28], general fatigue [27]	3364/16,496 [26]	5.2/252 [26]	5.7/10.1 [27]	13/829 [28]	11/325 [28]
3	28	1/1	39	VD	male	3226	None	None	None	3086/21,251 [26]	70/440 [26]	6/9.1 [28]	22/338 [28]	21/325 [28]

AST, asparatate transaminase; ALT, alanine transaminase; HBV; hepatitis B virus; HBe, Hepatitis B envelope; HBs, hepatitis B surface, GW; gestational week, CS; cesarean section, VD; vaginal delivery, Max; maximum, Preg; pregnancy.

clinical symptoms, such as itching and general fatigue. Although exacerbation of HBV infection is mostly asymptomatic and resolve spontaneously, some cases may be severe and result in symptomatic hepatic decompensation [3]. Therefore, if clinical symptom appears in HBs Ag-positive women during pregnancy, exacerbation of HBV infection should be considered. HBe Ag-positive is found to be a strong predictor of exacerbation of HBV infection during pregnancy, and HBe Ag-positive women have more than two-fold higher risk for a postpartum flare [8]. It has been reported that the frequency of exacerbation of HBV infection during pregnancy is 6% in HBs Ag-positive women [3,9], which is similar to 7.5% in the present study. In addition, in this study, serum baseline levels of AST, ALT, and HBV-DNA were not different between the HBe Ag-positive women with exacerbation of HBV infection during pregnancy and those without exacerbation. On the other hand, unexpectedly, baseline serum levels of HBs antigen in the HBe Ag-positive women with exacerbation were significantly lower than those without exacerbation, but the reason for this difference was unknown. In the present study, predictors for exacerbation of HBV infection during pregnancy in HBe Ag positive-women was not determined.

On the other hand, HBe Ag levels in the three cases with exacerbation of HBV infection increased to more than five times higher than prior to pregnancy. Simultaneously, levels of ALT and HBV-DNA also increased in the three cases. Therefore, monitoring for levels of HBe Ag, HBV-DNA, and liver enzymes as well as symptoms of itching and general fatigue is very important for HBs Ag-positive women during pregnancy and the postpartum period.

The guidelines of the American Association for the Study of Liver Diseases recommend antiviral medication with tenofovir in the third trimester for pregnant women with HBV-DNA >200,000 IU/ml or $>10^6$ copies/ml and higher, even in the absence of clinical symptoms, to reduce perinatal transmission of HBV [15]. Tenofovir has been shown to be safe during pregnancy and for breastfeeding mothers. In cases, where tenofovir is not effective, telbivudine or lamivudine may be substituted. There is no consensus on the management of HBV for women with blood HBV-DNA $\leq$200,000 IU/ml, women with active hepatic inflammation or advanced fibrosis, or who become pregnant while on therapy [15,16]. In the present study, none of the three cases with exacerbation of HBV infection received antiviral therapy, and the exacerbation resolved spontaneously. Exacerbation of HBV infection in the postpartum period occurs mostly during the first three months [3]. Thus, it is necessary to follow-up postpartum mothers closely for more than 3 months. Levels of liver enzymes and HBV-DNA should be repeatedly measured, especially in HBe Ag-positive women, because they are at a high risk for exacerbation of HBV infection in the postpartum period.

Potential conflicts of interest

All authors report no potential conflicts of interest.

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