Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.3504-19
Intern Med 59: 205-210, 2020
http://internmed.jp

【 CASE REPORT 】

The Administration of Tenofovir Disoproxil Fumarate for Pregnant Japanese Women with Chronic Hepatitis B

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Abstract:
The appropriate management of hepatitis B virus (HBV) infection during pregnancy has not been established in Japan. We herein report five HBV-infected pregnant Japanese women who received tenofovir disoproxil fumarate (TDF). Two of them had been born after the introduction of nationwide immunoprophylaxis and were vertically infected with HBV, highlighting the need to address mother-to-child transmission further. In both entecavir-experienced and nucleoside/nucleotide analog-naïve mothers, TDF suppressed HBV replication without serious adverse events. All five children were free from congenital disorders, growth impairment, and HBV infection. TDF showed safety and efficacy for pregnant woman with chronic hepatitis B and might have helped prevent mother-to-child transmission.

Key words: tenofovir disoproxil fumarate, hepatitis B virus, pregnancy, mother-to-child transmission

(Intern Med 59: 205-210, 2020)
(DOI: 10.2169/internalmedicine.3504-19)

Introduction

Chronic infections of hepatitis B virus (HBV) are estimated to affect 719,000 people or 0.6% of the general population (1) and contribute to approximately 10-15% of cases of cirrhosis (2) and liver cancer (3) in Japan. To reduce the burden of these serious hepatic complications on public health, it is essential to block mother-to-child transmission, one of the primary sources of chronic HBV infection. In 1986, the Japanese government implemented a nationwide policy to administer fixed-schedule hepatitis B immunoglobulin (HBIG) and hepatitis B vaccine (HB vaccine) to babies born to HBV-infected mothers in order to prevent mother-to-child transmission (4, 5). Initially, this preventive program targeted only mothers who were positive for both hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg), but it was modified in 1995 to cover all mothers who were positive for HBsAg, regardless of HBeAg status (6). This selective immunoprophylaxis dramatically reduced the prevalence of HBV carriers among children from 0.20-0.75% to 0.01-0.04% (4-6). However, universal vaccination was not implemented until 2016 in Japan (7).

Although chronic HBV infection typically remains stable during and after pregnancy, hepatitis flares occasionally occur in this period, presumably due to the dramatic hormonal and immunological alterations of pregnancy (8-12). The acute exacerbation is often self-limiting but may progress to hepatic decompensation or liver failure (8, 9, 11, 12). This is one of the reasons for the initiation or continuation of antiviral therapy for HBV-infected women during pregnancy (8-10, 13-15). Pregnancy is reportedly associated with an increased rate of spontaneous HBeAg seroconversion (16, 17), leading to the inactive phase of chronic HBV infection. Nonetheless, the adverse effects of antiviral therapy on the fetus, particularly with regard to teratogenicity, constitute serious concerns.

For the above reasons, pregnancy is an important point in the course of chronic HBV infection, both for pregnant women and the children born to them. However, there is little consensus regarding the appropriate management of pregnant women with chronic HBV infection in Japan. The guidelines for hepatitis B (version 3.1) published by the Japan Society of Hepatology (JSH) only mention that teno-

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Received for publication June 13, 2019; Accepted for publication July 29, 2019
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Table 1. Clinical Characteristics of Five Mothers Treated with TDF for Chronic Hepatitis B during Pregnancy (Cases 1–5).

Case no.	Age (years)	Birth year	G	P	HBV genotype	Infection route	Prior IFN	Prior NA	HBeAg at pregnancy	Initiation of TDF			Delivery		
										GA (weeks)	HBV-DNA (log IU/mL)	ALT (U/L)	GA (weeks)	Mode	Complication
1	21	1993	1	0	C	MTCT	IFN-β	ETV	+	7	<1.3	15	39	CS	-
2	30	1985	2	1	C	MTCT	-	ETV	-	(before this pregnancy)			40	VD	-
3	31	1985	3	1	C	(unknown)	-	-	+	33	>8.2	779	39	VD	-
4	27	1989	1	0	C	MTCT	-	-	+	31	8.1	228	39	VD	-
5	41	1975	1	0	C	MTCT	Peg-IFN	-	-	40	7.0	19	41	CS	NRFS

TDF: tenofovir disoproxil fumarate, G: gravidity, P: parity, HBV: hepatitis B virus, MTCT: mother-to-child transmission, IFN: interferon, Peg-IFN: pegylated interferon, NA: nucleoside/nucleotide analogue, ETV: entecavir, HBeAg: hepatitis B e antigen, GA: gestational age, ALT: alanine aminotransferase, CS: Caesarian section, VD: vaginal delivery, NRFS: non-reassuring fetal status

fovir disoproxil fumarate (TDF) is recommended over the other two first-choice nucleoside/nucleotide analogues (NAs) of entecavir (ETV) and tenofovir alafenamide (TAF) for women who are pregnant or wish to become so (18). Furthermore, the available data regarding the use of TDF for Japanese pregnant women infected with HBV are limited to situations that are not representative of daily clinical practice (19, 20).

We herein report five Japanese women who were treated with TDF for chronic hepatitis B during pregnancy and evaluate its efficacy and safety for pregnant women and the children born to them.

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Maternal courses

In all five women, TDF 300 mg once daily was orally administered during pregnancy and after delivery to treat chronic hepatitis B, as a component of daily clinical practice; they did not breastfeed, as advised on the package insert. The clinical characteristics of these women are shown in Table 1, and their individual courses until the end of 2017 are depicted in Figure.

The women ranged in age from 21 to 41 years old. Two had been born after the implementation of the national prevention program for mother-to-child transmission of HBV, which commenced in 1986 (Cases 1 and 4). Three were primigravida (Cases 1, 4, and 5), one was gravida 2, para 1 (Case 2), and one was gravida 3, para 1 (Case 3). All had HBV genotype C; the infection route was identified as mother-to-child transmission through a patient interview in all cases except for Case 3. Two had a history of interferon therapy (Cases 1 and 5), and two had been treated with ETV for a history of chronic active hepatitis (Case 1) or postpartum hepatitis flare after the delivery of a previous child (Case 2). Two achieved HBeAg seroconversion either spontaneously (Case 5) or during ETV therapy (Case 2).

Two women were administered TDF before pregnancy (Case 2) or in the first trimester (Case 1) by switching from ETV. In Case 2, TDF replaced ETV 9 months before the second pregnancy, reflecting the woman's desire to carry another child, and continued throughout the pregnancy. In Case 1, the patient became incidentally pregnant while taking ETV; she discontinued ETV, based on her own judgment, and switched to TDF at 7 weeks of gestation. In both women, ETV had reduced the HBV-DNA load to near or below the lower detection limit; this was maintained by subsequent TDF therapy.

The other three NA-naïve women started TDF for hepatitis flares (Cases 3 and 4) or HBV reactivation (Case 5) in the third trimester. In Cases 3 and 4, the women had persistently high viremia and received TDF when their respective serum alanine aminotransferase (ALT) levels rose to 779 U/L at 33 weeks and 228 U/L at 31 weeks of gestation. In particular, Case 3, who had been in the immunotolerant phase, presented with hepatic decompensation, as suggested by elevated serum total bilirubin levels (5.4 mg/dL) and decreased prothrombin activity (64%). In Case 5, as the pregnancy approached full-term, the maternal HBV-DNA levels gradually increased to 7.0 log IU/mL at 40 weeks of gestation, when TDF was introduced. As expected, hepatitis flare occurred in the perinatal period with maximal serum ALT levels of 169 U/L; this was milder than most of the previous flares the patient had experienced. Following the initiation of TDF, the maternal HBV-DNA load decreased below the detection limit at 7 months (Case 3), 8 months (Case 4), and 4 months (Case 5).

All women had singleton deliveries between 39 and 41 weeks of gestation. The modes of delivery were normal vaginal delivery in three (Cases 2, 3 and 4) and elective Caesarean section because of contractive pelvis (Case 1) and emergent Caesarean section due to a non-reassuring fetal status during labor induction (Case 5). During the follow-up period, none of the women exhibited any symptoms or laboratory abnormalities possibly related to TDF.

Outcomes of children

Every child received standard neonatal care, including immunoprophylaxis with HBIG and HB vaccine immediately after birth and HB vaccine at one and six months of age, in accordance with the guidelines of the Health and Labor Ministry of Japan. The birth weight, Apgar score (1 and 5 minutes), birth defects, growth problems, and mother-to-

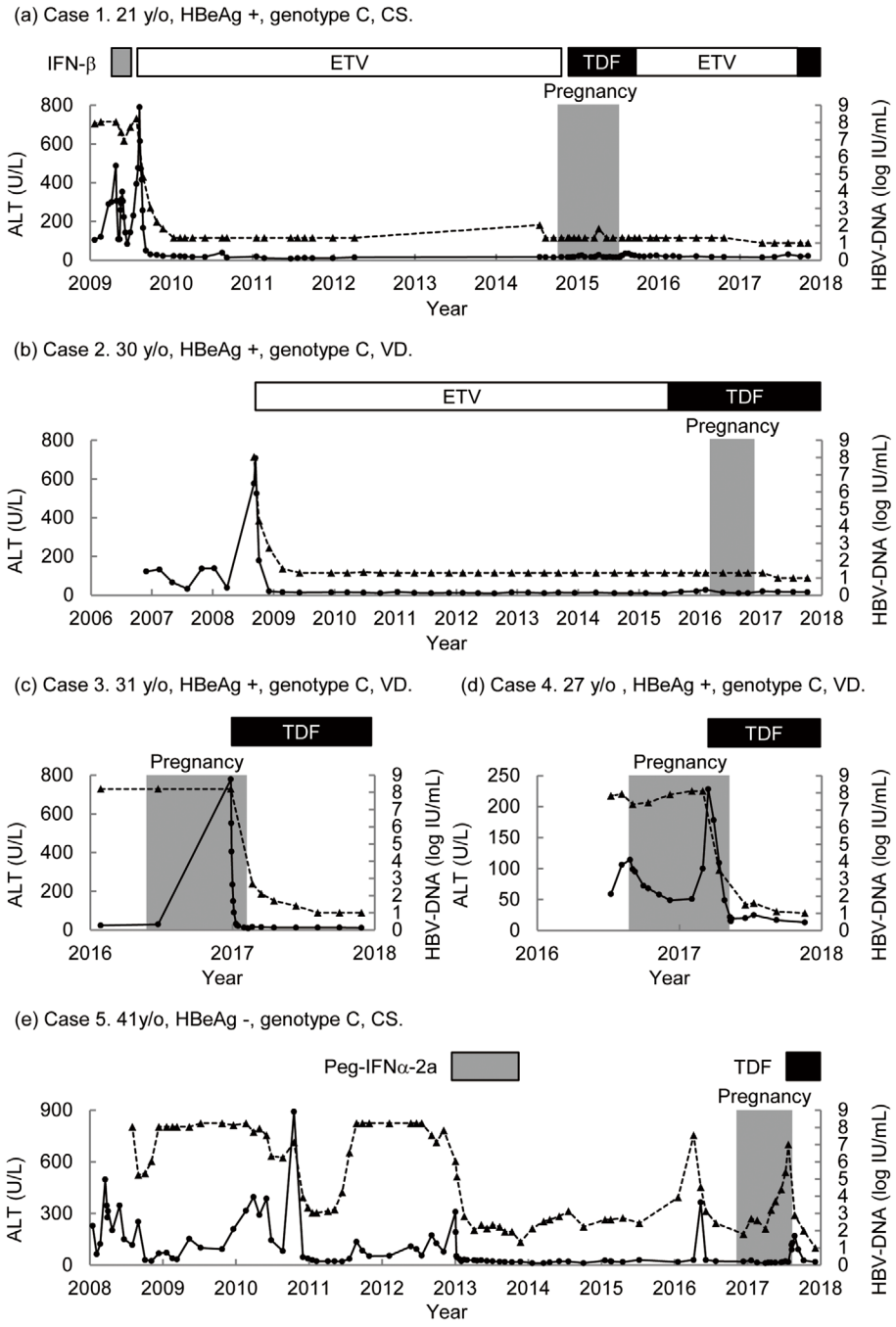

Figure. **The maternal courses of five pregnant women treated with TDF for chronic hepatitis B (Cases 1-5). Solid circle with solid line: serum ALT level, solid triangle with dotted line: serum HBV-DNA level. TDF: tenofovir disoproxil fumarate, ALT: alanine aminotransferase, HBV: hepatitis B virus, HBeAg: hepatitis B e antigen, CS: Caesarian section, IFN: interferon, ETV: entecavir, VD: vaginal delivery, Peg-IFN: pegylated interferon**

child transmission of HBV are shown in Table 2. The number of each child corresponds to that of the child's mother. In summary, all infants exhibited normal growth and did not acquire HBV infection during the observation period.

Discussion

This real-world clinical case series showed that TDF was safe and effective for pregnant Japanese women with chronic hepatitis B and the children born to them. Furthermore, TDF successfully suppressed HBV replication in both NA-naïve and ETV-experienced women. Except for one patient who underwent emergent Caesarian section for a non-reassuring fetal status during labor induction, none of the mothers in this study experienced serious obstetric complications or adverse events related to the administration of TDF. Furthermore, no children, including two who were exposed to TDF in the organogenetic period, developed congenital anomalies or growth impairments during the follow-up period.

Table 2. Outcomes of Infants Who Were Born to HBV-infected Mothers Treated with TDF during Pregnancy.

Case no.	Sex	Birth weight (g)	Apgar score (1/5 minutes)	Birth defect	Growth problem	At birth		After immunoprophylaxis			MTCT
						HBsAg	HBV-DNA	Age (weeks)	HBsAg	HBV-DNA	
1	M	3,296	8/9	-	-	-	-	38	-	-	-
2	M	3,585	8/9	-	-	(data not available due to delivery at other hospital)					-
3	M	3,209	8/9	-	-	-	-	53	-	-	-
4	M	3,206	8/9	-	-	-	-	34	-	-	-
5	F	3,056	8/9	-	-	-	-	37	-	(not tested)	-

The number of each child corresponds to that of the child's mother. HBV: hepatitis B virus, TDF: tenofovir disoproxil fumarate, M: male, F: female, HBsAg: hepatitis B surface antigen, MTCT: mother-to-child transmission

Critical considerations when administering antiviral therapy during pregnancy are the safety of the fetus and mother, as well as the efficacy of inhibiting maternal viral replication. In such cases, a potent NA with validated fetal safety must be selected because interferon therapy is contraindicated for use during pregnancy (14, 21, 22). Studies of antiviral therapy for pregnant women infected with human immunodeficiency virus supported that specific NAs were not associated with teratogenicity. According to the Antiretroviral Pregnancy Registry, there are sufficient data to evaluate the safety of lamivudine (LAM) and TDF; neither has been shown to increase the risk of birth defects in any trimester (23). Although breastfeeding while taking these NAs is discouraged according to the package inserts of each drug in Japan, it is not regarded as a contraindication overseas (21, 22, 24). The underlying rationale is that the level of these drugs secreted in breast milk is lower than the level that the fetus is exposed to *in utero* and thus is unlikely to be hazardous to infants. Of those two NAs, TDF is preferable to LAM, based on its high antiviral activity and genetic barrier against HBV (14, 21, 22). Despite concerns over the bone mineral density and renal function, there is a lack of safety warnings to withhold TDF during pregnancy for both mothers and infants born to them (25, 26). However, TAF, an equally powerful NA with improved bone and renal safety compared to TDF (27), has not been studied in pregnant women (21). Therefore, the evidence concerning the safety and efficacy profile of TAF in this setting is insufficient at present. Overall, antiviral therapy with TDF should be carefully considered for use in HBV-infected mothers who need such treatment, although the specific indications have not been firmly established. As described previously, JSH only refers to the drug of choice and does not provide details regarding patient selection or the timing of treatment (18). The American Association for the Study of Liver Diseases (AASLD) states that the treatment approach for pregnant women infected with HBV is similar to that in non-pregnant patients (21); in contrast, the European Association for the Study of Liver (EASL) has a more cautious perspective, advising treatment deferral until delivery in women without advanced fibrosis or cirrhosis (22).

The varied courses of the women with chronic HBV infection described in this report provide insight into the use of TDF treatment for women of childbearing age. If non-pregnant women with active hepatitis wish to conceive but require NA therapy, TDF should be introduced before pregnancy (22). While childbearing must be carefully planned in women who are using NA therapy, such women can become unintentionally pregnant. It should be noted that the withdrawal of antiviral agents during pregnancy frequently induces HBV reactivation and hepatitis flares (15, 28), whereas no flares occur if antiviral therapy is continued throughout pregnancy (15). Therefore, to prevent hepatitis flares, it is advisable to continue or switch to TDF once the pregnancy is noted, provided the mother accepts the safety profile of TDF (14). Untreated women in the immunotolerant or immunoactive phase may develop acute exacerbation during pregnancy; in such cases, TDF should be considered based on the severity of hepatitis (13, 14). Even if the maternal course is uneventful, HBV-infected women should be regularly monitored for postpartum flares, which may require antiviral therapy (8, 9).

Our report of HBV-infected mothers emphasizes the need to address mother-to-child transmission in modern Japan further. The presence of chronic HBV infections in women born after the initiation of the preventive program who nonetheless acquired HBV from their mothers indicates that immunoprophylaxis alone cannot eliminate mother-to-child transmission. This finding is supported by the results of epidemiological studies, which have shown that mother-to-child transmission remains the most common cause of chronic HBV infection among Japanese people born after the preventive program was started (29, 30). Because incomplete immunoprophylaxis can result in mother-to-child transmission (31), the Japanese government simplified the vaccination schedule in 2013; this simplified schedule was used for the babies born to mothers in this report. However, there are many other known mechanisms of immunoprophylaxis failure, such as intrauterine infection (31, 32), HBsAg mutation (33, 34), and horizontal infection of the mother during pregnancy (31). Previous studies have indicated that a high maternal viral load is a risk factor for immunoprophylaxis failure (32, 35, 36). Thus, the presence of high viremia in the NA-naïve mothers in the present report serves as evidence that there remain Japanese women who can vertically transmit HBV to their children. Notably, while one mother

had immunoprophylaxis failure, the other two were born before the introduction of the preventive program.

In addition to its principal purpose of treating maternal hepatitis, administration of TDF might have aided in preventing mother-to-child transmission. Both AASLD and EASL recommend antiviral therapy in combination with immunoprophylaxis for highly viremic pregnant women in order to reduce mother-to-child transmission of HBV (21, 22). Using this strategy, NA (preferably TDF) is administered to pregnant women with HBV-DNA >200,000 IU/mL, beginning in the late second or early third trimester and continuing until delivery or postpartum; the newborn then receives standard immunoprophylaxis with HBIG and HB vaccine. A number of prospective comparative studies (37, 38) and randomized controlled trials (39, 40) conducted overseas have shown that TDF significantly reduced the maternal viral load and mother-to-child transmission without increasing the incidence of clinically meaningful adverse events. However, a double-blind randomized controlled trial in Thailand suggested that if mother-to-child transmission was well controlled by immunoprophylaxis alone, the additional effect of TDF was not found to be statistically significant (0% in the TDF group vs. 2% in the placebo group) (41). In the preventive program implemented in Japan, the rates of immunoprophylaxis failure in prefecture-based studies were reportedly 0-6.5% during the late 1980s and early 1990s (4, 5); however, more recent nationwide data are unavailable. Thus far, the true advantage of adopting this strategy in Japan remains unclear; nonetheless, TDF should be appropriately delivered to HBV-infected pregnant women with valid reasons for treatment of liver disease, which is an approach that can also help prevent mother-to-child transmission.

In conclusion, we reported five cases of Japanese women with chronic hepatitis B who underwent TDF therapy during pregnancy. TDF was safe and effective for pregnant women with chronic HBV infection and the children born to them. Mother-to-child transmission of HBV remains a serious public health issue that is yet to be addressed fully in Japan. Considerations regarding antiviral therapy for HBV-infected women of childbearing age should include treatment of maternal liver disease and prevention of mother-to-child transmission.

The study protocol was approved by the ethical committees of Osaka City General Hospital and Osaka City University Hospital and conducted in accordance with the amended Declaration of Helsinki. Informed consent was waived due to the retrospective nature of the study.

Author's disclosure of potential Conflicts of Interest (COI).
Norifumi Kawada: Honoraria, Gilead Sciences; Research funding, Gilead Sciences.

Acknowledgement

We thank the obstetricians and pediatricians of Osaka City General Hospital for caring for the mothers and children in this study.

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