


# Entecavir administration to pregnant Japanese woman with chronic hepatitis B and hepatocellular carcinoma: A case report

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## Abstract

Women taking entecavir hydrate (ETV) may not need to consider abortion in the event of an unexpected pregnancy. If a woman with renal dysfunction and taking ETV for chronic hepatitis B becomes pregnant, continuous use of ETV may also be tolerated.

## KEY WORDS

entecavir hydrate, hepatitis B virus, pregnant, tenofovir disoproxil fumarate

## 1 | INTRODUCTION

The World Health Organization estimates that there are approximately 257 million people with persistent hepatitis B virus (HBV) infection worldwide and that >887,000 people die each year from HBV-induced liver damage.<sup>1</sup> In Japan, the HBV mother-to-child transmission (MTCT) prevention project started as a national project in 1986 and has implemented selective vaccination of anti-hepatitis B surface antigen (HBs-Ag) human immunoglobulin and HBV vaccine for children born to mothers of HBV carriers.<sup>2</sup> Consequently, the number of MTCT cases has rapidly decreased. However, 5% of offspring from hepatitis B envelope antigen (HBe-Ag)-positive pregnant women become HBV carriers even if preventive measures are taken, which is a very important problem.<sup>3</sup>

Reduction of the HBV viral load during delivery by oral administration of nucleoside/nucleotide analogs (NAs) in late pregnancy reportedly reduces MTCT.<sup>4-6</sup> A maternal HBV-DNA level of  $\geq 10^7$  copies/mL is reportedly a high risk of HBV MTCT.<sup>7</sup> In Japan, lamivudine (LAM), adefovir pivoxil (ADV), entecavir hydrate (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) as NAs are covered by insurance for chronic HB (CHB). The guidelines

for HB (version 3.2) published by the Japan Society of Hepatology only mention that TDF is recommended over the other two first-choice NAs of ETV and TAF for women who are pregnant or wish to become so.<sup>8</sup> According to the US Food and Drug Administration's criteria for drug fetal risk classification, LAM and ETV are classified into category C where it is not possible to deny the risk, and TDF is classified into category B where there is no evidence of fetal risk in humans.<sup>9</sup> For TAF, there is no evidence of fetal safety.<sup>8</sup>

We report a case of a Japanese child born to a mother treated with ETV for CHB and hepatocellular carcinomas (HCCs) during pregnancy when TDF was not approved for treatment of chronic hepatitis by public insurance in Japan.

## 2 | CASE PRESENTATION

### 2.1 | Maternal course

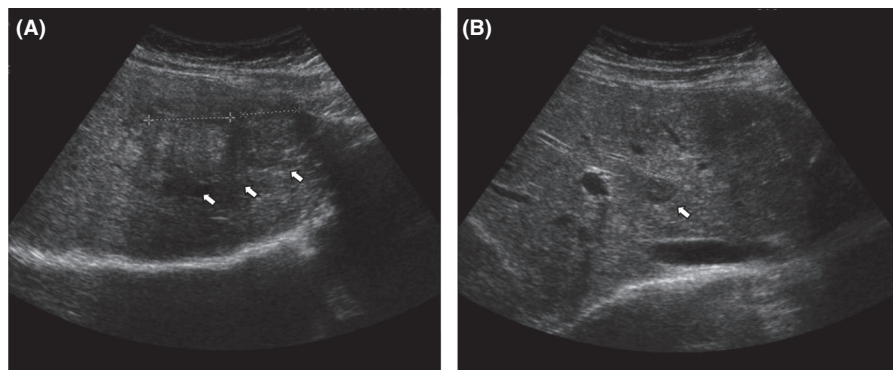
A 30-year-old woman gave birth to a second healthy boy. At age 23, she tested positive for the HBs-Ag at a prenatal checkup and became pregnant with her first baby boy. Her mother and maternal uncle and his wife and child were HBV carriers. At that time, her husband was admitted to our

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**TABLE 1** Blood test and biochemical test results at diagnosis

Blood test biochemical test					
WBC	6200	/ $\mu$ L	TP	7.3	g/dL
Neu	59.6	%	Alb	4.4	g/dL
Lym	31.4	%	T-Bil	0.4	mg/dL
Mo	6.6	%	D-Bil	0.0	mg/dL
Hb	13.9	g/dL	AST	21	IU/L
Plt	$195 \times 10^3$	/ $\mu$ L	ALT	27	IU/L
			LDH	138	IU/L
HBs-Ag	236.3	IU/mL	ALP	381	IU/L
HBs-Ab	0.2	mIU/mL	GGT	15	IU/L
HBe-Ag	0.3	S/CO	CRP	0.04	mg/dL
HBe-Ab	99.7	%Inh			
HBV-DNA	3.6	Log IU/mL	AFP	699	ng/mL
Wild type	100	%	L3	4.0	%
Geno type	C		PIVKA-II	521	mAU/mL

**FIGURE 1** Abdominal ultrasonography findings. White arrows indicate the hepatocellular carcinomas

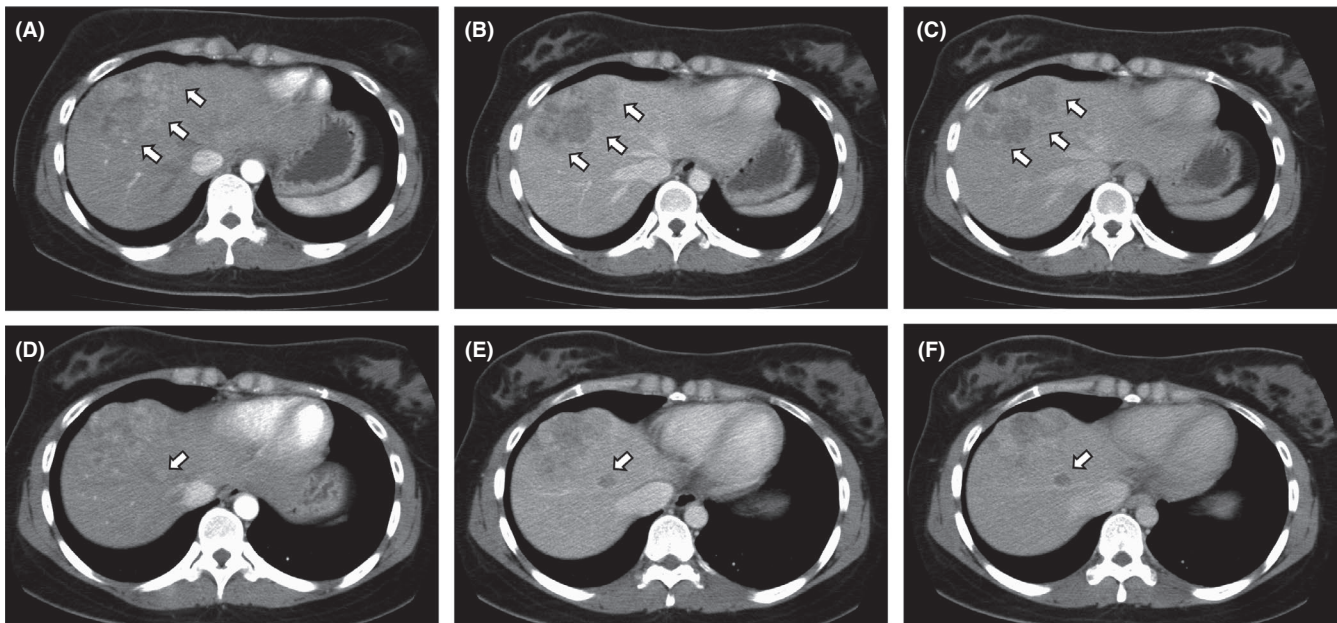
hospital for HBV acute hepatitis. At the third month after giving birth, she had a detailed examination for hepatitis. Table 1 shows the results of blood tests. Laboratory findings revealed a total bilirubin level of 0.4 mg/dL, a serum aspartate aminotransferase level of 21 IU/L, and a serum alanine aminotransferase level of 27 IU/L. Her Child-Pugh classification was grade A (score 5). She was positive for HBs-Ag (236.3 IU/mL; normal range, <8 IU/mL), HBe-Ab (99.7%Inh; normal range, <60%Inh), and HBV-DNA in her serum. Her HBV-DNA level was 3.6 log IU/mL (normal range, negative) and HBV genotype was type C. Serum HBs-Ab (normal range, <10 mIU/mL) and HBe-Ag (normal range, <1.0 S/CO) were negative. Ultrasonographic and computed tomographic results revealed 2-cm and 8-cm diameter HCCs in the segment 4 and 8 areas at that time (Figures 1 and 2). The tumor markers' alpha-fetoprotein (AFP: 699 ng/mL; normal range, <20 ng/mL) and protein induced by vitamin K absence or antagonist II (PIVKA-II: 521 mAU/mL, normal range, <40 mAU/mL) were also positive. Immediately, the surgeon performed a resection of the same site, and then the anticancer drug (cisplatin and 5-fluorouracil) and ETV (0.5 mg/d) were started. Her liver

tissue was evidence of CHB (Ishak score: A1, F1).<sup>10</sup> Her operation was able to safely remove the HCCs, and ETV was continued after the operation.

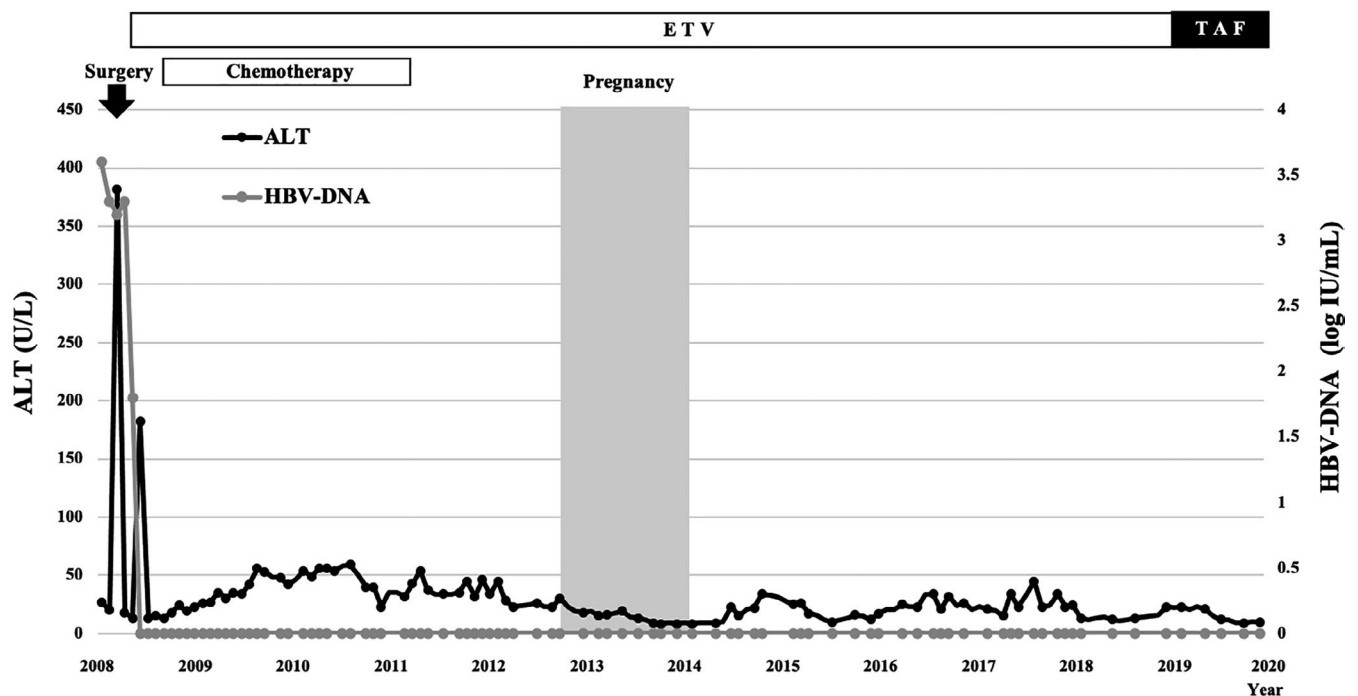
Figure 3 shows her clinical course. Six years after her first childbirth and treatment for HCCs, she became pregnant at age 30 with a second child. During that time, she continued to undergo strict follow-up and to take ETV internally under a hepatologist. Fortunately, she had no recurrence of HCCs. She was 2 months pregnant and taking ETV for CHB when she realized she was pregnant. She and her husband strongly desired to stay pregnant. At that time, her physician's evaluation found that it was difficult to discontinue the NAs for chronic hepatitis, so he allowed her to continue with her pregnancy and delivery without stopping ETV. At that time, the use of TDF for medical treatment was not covered by public insurance in Japan.

## 2.2 | Outcomes of the child

At 41 weeks and 1 day of gestation, the delivery date had been exceeded and she exhibited temporary bradycardia, so



**FIGURE 2** Abdominal contrast-enhanced computed tomography findings. A, D, Hepatic artery phase; (B, E) Portal venous phase; (C, F) Equilibrium phase. White arrows indicate the hepatocellular carcinomas



**FIGURE 3** Maternal clinical course. ETV, entecavir hydrate; TAF, tenofovir alafenamide; ALT, alanine aminotransferase; HBV, hepatitis B virus

the baby was delivered by emergency Cesarean section. Her child, a boy, weighed 3372 g. His Apgar score was 8 (1 minute) and 8 (5 minute), and no special treatment was required; only standard treatment for newborns was performed. The baby's blood test results and his head, heart, and abdominal ultrasonography results were also normal (Table 2A). He had no external malformations and was diagnosed as a normal neonate by a neonatologist. Because his mother had

to continue taking ETV after giving birth, he was only fed full formula milk, not breast milk. To prevent HBV MTCT, hepatitis B (HB) globulin and HB vaccine were administered immediately after birth. Additionally, HB vaccine was readministered 1 and 6 months after birth. At 10 months after birth, the HBs-Ag test result was negative, and the HBs-Ab titer increased to 339 IU/mL, confirming successful HB preventive treatment.

**TABLE 2** (A) Blood test results of the child at birth and at 5 years of age. (B) Other blood test results at 5 years of age

	0-year-old	5-year-old	
<b>(A)</b>			
WBC	13 400	5300	/ $\mu$ L
Hb	14.5	12.1	g/dL
Plt	$154 \times 10^3$	$281 \times 10^3$	/ $\mu$ L
TP		6.7	g/dL
Alb		4.1	g/dL
T-Bil	2.0	0.5	mg/dL
D-Bil		0.1	mg/dL
AST	21	41	IU/L
ALT	25	16	IU/L
LDH		315	IU/L
ALP		673	IU/L
GGT		10	IU/L
BUN		12.0	mg/dL
Cre		0.3	mg/dL
Na		137	mEq/L
K		4.3	mEq/L
CRP	1.33	0.02	mg/dL
	5-year-old	Normal range	
<b>(B)</b>			
GH	1.62	0.00-2.47	ng/mL
IGF-1	107	44-193	ng/mL
TSH	2.18	0.50-5.00	$\mu$ IU/ mL
free-T3	4.6	2.3-4.0	pg/mL
free-T4	1.2	0.9-1.7	ng/dL
ACTH	13.7	7.20-63.30	ng/mL
Cortisol	4.49	6.20-18.00	$\mu$ g/dL
HBs-Ag	0.00	<0.03	IU/mL

The medical checkups at age 1, 1.5, 2, and 3 years did not reveal any obvious abnormal findings by a pediatrician. At age 6, he underwent blood testing (Tables 2A,B), heart and abdominal ultrasonography, physique evaluation, and developmental evaluation (Wechsler Intelligence Scale for Children—Fourth Edition, Full Scale Intelligence Quotient = 91), but no abnormal findings were found overall. His 6-year height and weight gain were also normal (Figure 4). We judged that he was a normal child, and he continues to grow and be healthy.

### 3 | DISCUSSION

In this case, a Japanese child was born to a mother treated with ETV for CHB and HCCs during pregnancy, and we

were able to observe the long-term health over 6 years of the child. Kakogawa et al<sup>11</sup> reported a CHB pregnant woman successfully treated by ETV. To our knowledge, this is the first report of a patient treated with ETV for CHB with acute exacerbation during her pregnancy and the second case report of ETV exposure during the fetal period. An important aspect of this case is that we were able to perform long-term evaluation of the child up to age 6 years who was born to a woman during treatment with ETV.

Decisions about initiating treatment for HBV infection during pregnancy must be made after considering the risks and benefits of the mother and fetus. Data on the safety of antiviral treatment of HBV during pregnancy remain limited.<sup>11</sup> From the mother's point of view, although CHB typically remains stable during and after pregnancy, the acute exacerbation may progress to hepatic decompensation or liver failure.<sup>12,13</sup> From the child's point of view, the adverse effects of NAs on the fetus, particularly regarding teratogenicity, constitute serious concerns.<sup>9</sup> There is less clinical experience with the use of ETV during pregnancy despite its higher resistance barrier relative to that of LAM. In the treatment guidelines for hepatitis B of the Japan Society of Hepatology, ETV is not suitable for long-term continuous treatment of women who wish to have children because of the risk of teratogenicity.<sup>8</sup> According to the recommendations from the American Association for the Study of Liver Disease (AASLD), the European Association for the Study of the Liver (EASL), and the Asian Pacific Association for the Study of the Liver, TDF should be continued while ETV or other NAs should be switched to TDF in pregnant women already on NAs therapy.<sup>14-16</sup> Among the currently available NAs, LAM, and TDF are classified as category B drugs (no risk in animal studies, but unknown risk in humans), whereas LAM, ADV, and ETV are classified as category C drugs (teratogenic in animals, but unknown risk in humans) according to the US Food and Drug Administration's criteria. In pregnant females with chronic HBV infection who need antiviral therapy, TDF is the drug of choice for mothers indicated for antiviral treatment during the first through third trimesters of pregnancy.<sup>16</sup> Safety data from the Antiretroviral Pregnancy Registry shows no increased rates of birth defects (2.8%, 46/1982) with TDF exposure during the first trimester.<sup>17</sup> However, there is concern about the potential for TDF to cause nephrotoxicity. For TAF, there is no evidence of fetal safety.<sup>8</sup>

Although there are no definite conclusions about the risk of TDF-associated nephrotoxicity, it has been recommended that this agent be avoided in this setting.<sup>16</sup> TDF may be associated with proximal tubular mitochondria disorders followed by hypophosphatemia and even glomerular disorders.<sup>18</sup> Like TDF, ETV is positioned as a first-line drug for NAs in the treatment of CHB and has no major anxiety other than the risk of teratogenicity.<sup>8,14-16</sup> In

### Transverse standard height and weight curve in Japanese male (0-16year)

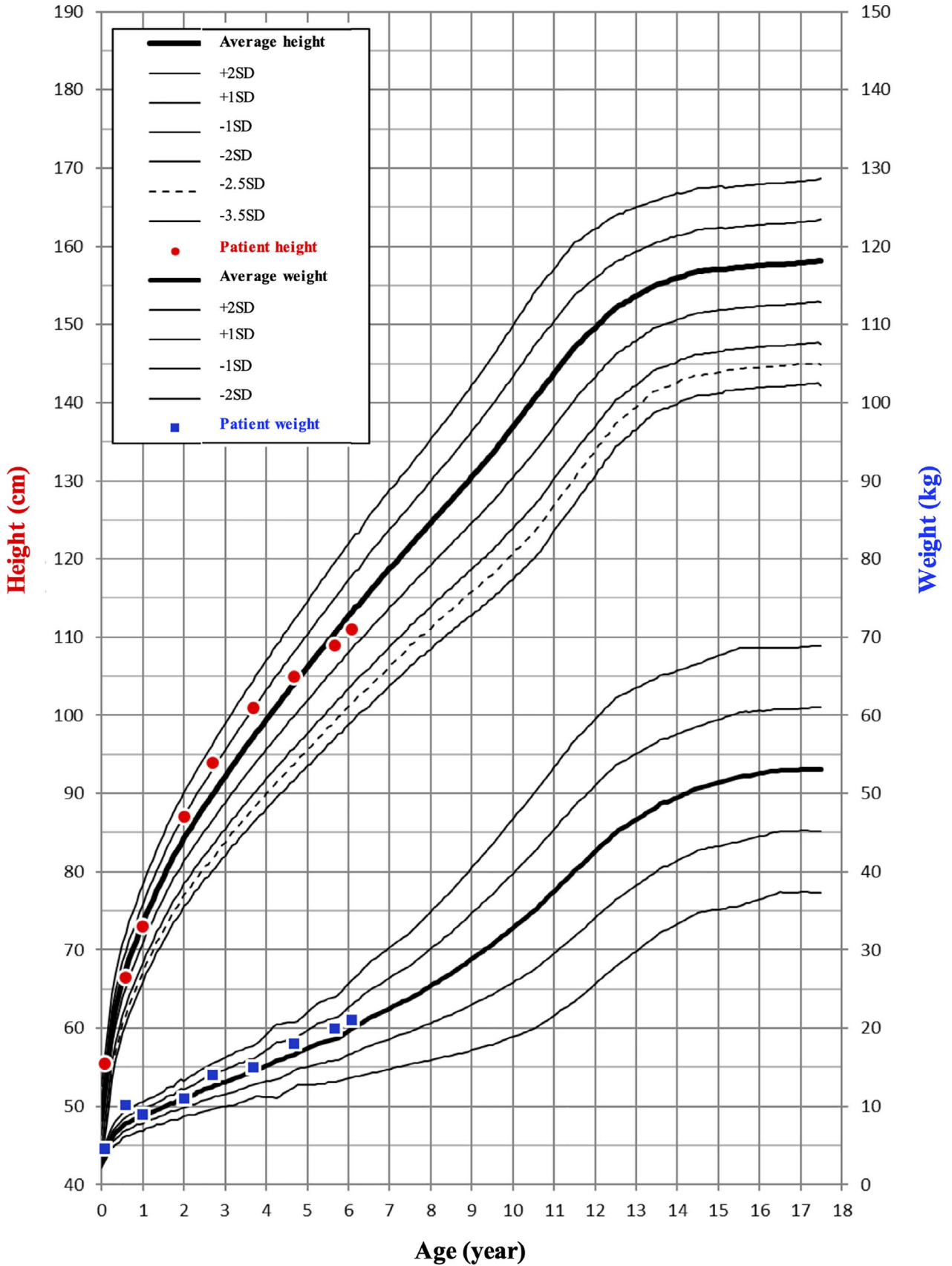


FIGURE 4 His growth curve. The child's height and body weight were in the normal ranges. SD, standard deviation

the present case, a child born to a woman who took ETV during the entire pregnancy was healthy for the 6-year follow-up period, so if a woman with renal dysfunction and taking ETV becomes pregnant, continuation of ETV and not changing to TDF may be an option. The use of LAM in such circumstances does not appear to be superior to ETV because of tolerance issues.

Both the AASLD and EASL recommend antiviral therapy in combination with immunoprophylaxis for highly viremic pregnant women to reduce MTCT of HBV.<sup>14,15</sup> A number of prospective comparative studies<sup>6</sup> and randomized controlled trials<sup>19</sup> conducted overseas have shown that TDF significantly reduced the maternal viral load and MTCT without increasing the incidence of clinically meaningful adverse events. Funk et al<sup>20</sup> reported that they found evidence to support the efficacy and safety of peripartum antiviral prophylaxis using TDF, LAM, and telbivudine. However, although ETV was not used in all studies and the success or failure of HBV MTCT prevention was evaluated, the born child received little long-term evaluation. The value of our case is that we followed the child for 6 years during which we performed physical and mental development, the results of which should be useful to physicians and caregivers of children born to mothers who took NAs for their entire pregnancy.

In conclusion, our findings from this single case may help reduce the worry that women taking ETV will have to consider abortion in the event of an unexpected pregnancy. If a woman with renal dysfunction and taking ETV for CHB becomes pregnant, continuous use of ETV may be acceptable, as our case shows. However, accumulation of cases, if possible, is necessary to strengthen the evidence for continuation of ETV during pregnancy in women with renal dysfunction.

#### 4 | DATE AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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#### CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. There was no external funding in the preparation of this manuscript.

#### AUTHOR CONTRIBUTIONS

Dr Kakiuchi T: involved in patient care as well as the drafting, review, and revision of the initial manuscript. Dr Takahashi H: involved in patient's treatment decision as well as the review and revision the initial manuscript. Dr Iwane S and Dr Koji Ainvolved in patient care as well as the review and revision of the initial manuscript. Dr Matsuo M: involved in patient care and project administration as well as the review and revision of the initial manuscript. All authors approved the final manuscript submission and agree to be accountable for all aspects of the study.

#### ETHICAL APPROVAL

Ethical review and approval of the study on human participants in accordance with the local legislation and institutional requirements was not required in this case. Written informed consent to publish this case was provided by the patient herself and the patient's legal guardian/next of kin.

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