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Safety of entecavir antiviral therapyduring an accidental pregnancy in patients with chronic hepatitis B

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Abstract. The present study aimed to investigate the effects of accidental pregnancy CHB patients' reproductive age on their offspring during entecavir (ETV) antiviral therapy. A total of 112 couples were retrospectively enrolled, and they were divided into an observational and control group. A total of 53 couples who had accidental pregnancies while receiving long-term ETV antiviral medication were recruited for the observational group. The control group consisted of 59 couples who became pregnant accidentally while receiving long-term tenofovir disoproxil fumarate (TDF) antiviral treatment. All mothers persisted in their pregnancies in the observational group, and ETV was promptly replaced with TDF. Every mother remained pregnant and continued to use TDF in the control group. The maternal and baby safety profiles, including the prevalence of congenital disabilities, were comparable across the observational and control groups at delivery. In addition, no unusual indications or symptoms of the newborns were noted during the follow-up intervals of 28, 48, and 96 weeks postpartum. Initiating ETV or TDF in early and middle pregnancy seems safe for mothers and infants. Important data from the present study support using ETV in early-mid gestational accidental pregnancies and the prompt substitution of TDF antiviral medication for ETV.

Introduction

Hepatitis B virus (HBV) infection is a global epidemic, and the severity of the epidemic varies widely by region. According to the WHO report, there were ~296 million chronic HBV infections globally in 2019 (1). In China, the prevalence of hepatitis B surface antigen (HBsAg) in the general population was 5-6% in 2019; >70 million people had chronic HBV infections, of which 20-30 million had chronic hepatitis B (2). Thus HBV infection still poses a severe threat to public health and is also linked to liver cancer and cirrhosis (3). Long-term antiviral treatment can lessen the severity of cirrhosis and the occurrence of liver cancer (3-6). As a result, long-term antiviral therapy has received significant attention, and mothers or fathers of childbearing age have experienced accidental pregnancies whilst receiving long-term antiviral therapy.

One of the first-line antiviral treatments for patients with chronic hepatitis B (CHB) is entecavir (ETV), which was generally approved by the US Food and Drug Administration (FDA) and Chinese FDA in 2005 (7-14). In clinical practice, there are accidental pregnancies during long-term ETV antiviral therapy, and the aim of the present study was to monitor the safety of the mothers and their offspring.

Materials and methods

Patients and study design. The present study was a retrospective cohort study. In Qinhuangdao Third Hospital (Qinhuangdao, China), patients were recruited from the hospital outpatient department following hospital admission. Between August 2016 and July 2020, 53 mothers in the observational group experienced accidental pregnancies while receiving long-term ETV antiviral medication, from which the mothers were selected and the HBV markers (HBVMs) were assessed. Eligible participants were pregnant mothers aged 21 to 31 years. The mean(±SD) maternal age was 24(±2.1) years, and the fathers were 22 to 33 years of age, with a mean(±SD) age of 26(±2.1) years. For the observational group, 13 mothers were positive for HBsAg, HBeAg, and antibodies against anti-HBc and HBV DNA (24.5%). The other 40 mothers were positive for HBsAg, anti-HBe, anti-HBc, or positive for HBsAg, anti-HBc, and HBV DNA negative (75.5%, 40/53). In total, 53 mothers had abnormal liver function; the liver function of the fathers was normal, and the HBVMs were as follows: 6 fathers were HBsAg-positive, HBeAg-positive,

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anti-HBc-positive, and HBV DNA-positive; and 5 fathers were HBsAg-positive, anti-HBe-positive, anti-HBc-positive and HBsAg-positive, anti-HBc positive, or HBV DNA negative. Among them, HBsAg-positive fathers accounted for 20.7% of the males in the observational cohort (11/53), 11 were receiving ETV antiviral therapy simultaneously, and the other 42 were HBsAg-negative.

In the control group, eligible participants were pregnant mothers aged 20 to 32 years. The mean(±SD) maternal age was 25(±2.2) years, and the fathers were 22 to 34 years of age, with a mean(±SD) age of 26(±2.2). 59 couples were selected who had an accidental pregnancywhilst taking long-term tenofovir disoproxil fumarate (TDF) antiviral therapy between August 2016 and May 2020, and the HBVMs of the mothers were assessed. For the control group, 17 mothers were detected as positive for HBsAg, HBeAg, anti-HBc, and HBV DNA (28.8%). The other 42 mothers were positive for HbsAg, anti-Hbe, anti-HBc, or positive for HbsAg, anti-HBc, and HBV DNA negative (71.2%). In total, 59 mothers exhibited abnormal liver function, The liver function of the fathers was normal, and the HBVMs were as follows: 6 cases HbsAg-positive, HbeAg-positive, anti-HBc-positive, HBV DNA-positive, and 9 cases HbsAg-positive, anti-Hbe-positive, anti-HBc-positive or HbsAg-positive, anti-HBc positive, and HBV DNA negative. HbsAg-positive fathers accounted for 25.4% of the males in the control cohort (15/59); 15 fathers received ETV antiviral therapy, whilst the other 44 fathers were HBsAg-negative.

The Ethical Committee of Qinhuangdao Third Hospital approved the present study (approval no. QHDSDSYYEC-3), and the need for informed consent was waived. The present study complied with the guidelines described in the Declaration of Helsinki (15). All the selected couples met the following criteria: i) Negative testing for serum hepatitis A, C, D, and E viruses and HIV, no alcoholic liver disease or autoimmune liver disease; ii) normal renal function; iii) mothers or fathers had a history of HBV ranging between 1-28 years; iv) newborn venous blood samples were collected at birth. Umbilical cord blood was defined as residual blood in the placenta and umbilical cord, and the fetal umbilical cord was ligated to prevent mixing with contaminating factors in the mother's blood. Factors potentially contaminating the umbilical cord blood included placenta previa, placental abruption, and other factors associated with cesarean delivery. Key exclusion criteria included the use of other HBV antiviral treatments as a monotherapy or in combination with ETV or TDF during the accidental pregnancy; participation in other clinical trials and the use of investigational regimens; co-infection with syphilis, toxoplasma gondii; evidence of hepatocellular carcinoma or cirrhosis; or a family history of genetic disease.

This study was retrospectively registered: Registration number, ChiCTR-OOC-16009151; Name of the registration, Clinical efficacy and Genotoxic effect of Entecavir; Date of registration, September 4, 2016).

Treatment. In the observational group, all mothers proceeded with their pregnancyafter they were selected to replace ETV (0.5 mg, once a day) immediately with TDF (300 mg, once a day) (10-13), 11 HBsAg-positive fathers continued to receive ETV (0.5 mg, once a day) antiviral therapy.

In the control group, all mothers proceeded with their pregnancy and continued the use ofTDF (300 mg, once a day) (10-13), and the 15 HBsAg-positive fathers continued with their use of ETV (0.5 mg, once a day) antiviral therapy.

All newborns received 100 IU hepatitis B immune globulin (HBIG) (Chengdu Institute of Biological Products) intramuscularly within 2 h of birth, plus 10 μg HBV vaccine (HBVac, recombinant yeast; Shenzhen KangtaiBiopharm Co., Ltd.) within 2 h of birth. The same doses HBVac were applied at 1 and 6 months postpartum (10-13,16,17).

Detection methods. Venous blood samples were collected in anti-coagulant tubes from the mothers, fathers and infants HBVMs, and assessed for the HBV DNA viral load. HBVMs and the HBV DNA viral load were measured using the same sample in the observation and control group, respectively. To assess HBVMs, an electrochemiluminescence method was used with an automatic electrochemiluminescence immunoassay analyzer (cobas-e-411 or 602; Roche Diagnostics, GmbH); HBV HBsAg, anti-HBs, HBeAg, anti-HBe and anti-HBc electrochemiluminescence detection kits were purchased from Roche Diagnostics, GmbH. The quantitative assessment of HBV DNA was performed by quantitative (q) PCR. PCR reagents, including HBV DNA quantitative fluorescence diagnostic kits, were provided by Hunan Shengxiang Biotechnology Co., Ltd. A quantitative PCR instrument (SLAN; Hunan Shengxiang Biotechnology Co., Ltd.) was used for thermocycling and concurrent detection, as described previously (18). Quality controlswere performed every 24 h at least, during which the kit was replaced.

Outcome measurements. The primary outcomeswere safety for mother-infant dyads, which included monitoring for adverse events, drug tolerability, obstetric complications, and congenital disabilities with or without ETV exposure. The congenital disability was defined as any major structural malformation in a fetus or infant during the prenatal or postnatal stages up to the agesof 28, 48, and 96 weeks.

The secondary outcomes were efficacy: i) Rates of mother-to-child transmission (MTCT); ii) cesarean section rates were included in the safety analysis (19); iii) effects of breastfeeding on the infants whilst TDF was taken by mothers; iv) direct effect of HBV infection on neonatal outcomes; and v) effects of pregnancy on neonatal outcomes whilst the fathers were taking ETV. The direct genome-sequencing method was used to monitor viral genotypic mutations in the patients in the study.

Statistical analysis. Patient data was collected from the medical records, which were anonymized before any analysis was performed. In the analysis of the rates of MTCT, all enrolled patients were included except if a case had incomplete data or waslost to follow-up. Descriptive variables are presented as the mean ± SD.A Student's t-test and χ^2 test were applied to compare the quantitative and categorical variables, respectively. When all expected counts were >5, a Pearson's χ^2 was used for categorical variables. When the expected count was <5, applied continuity remediation was used. $P<0.05$ was considered to indicate a statistically significant difference. All data were analyzed using SPSSversion 24.0 (IBM Corp.).

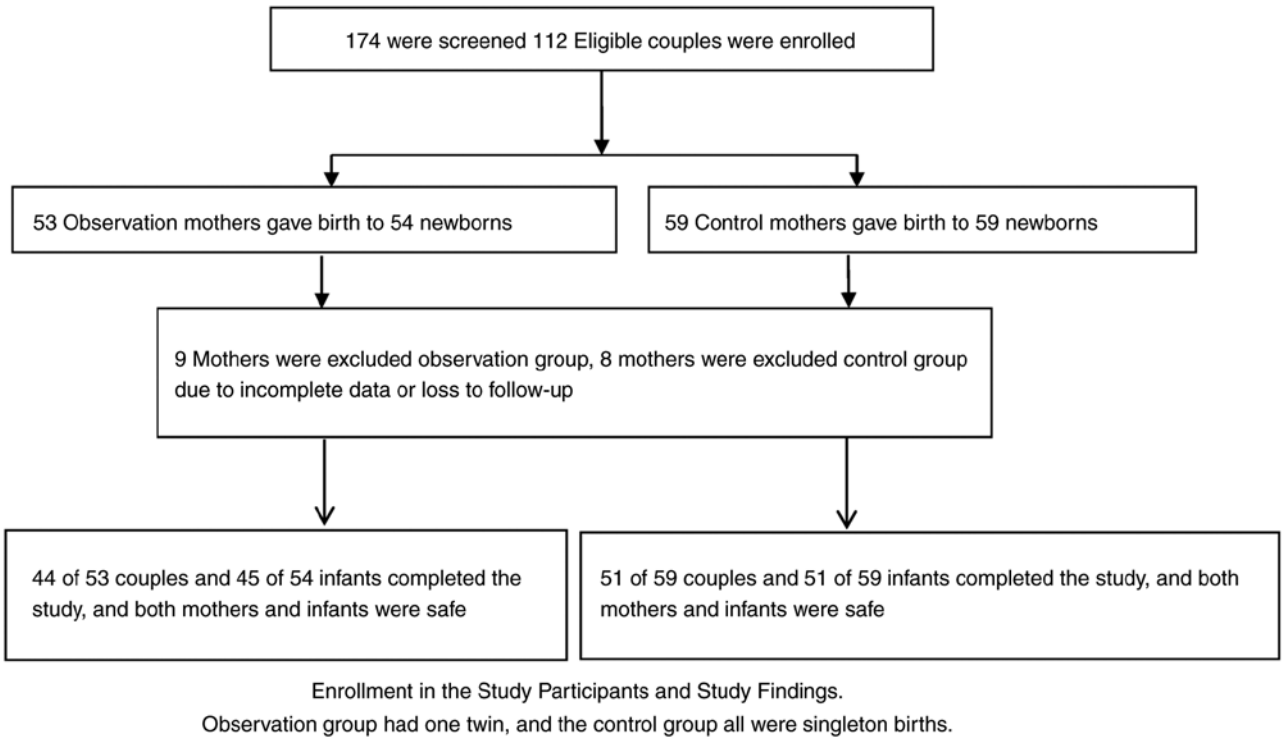

Figure 1. Enrollment of the participants and the study findings. The observation group had one pair of twins, and the control group all were singleton births.

Results

Participants. Among the 174 couples and infants screened, 53 couples and infants were deemed eligible and were enrolled into the observational group; that is, they were receiving long-term ETV anti-viral therapy. Among them, there were 14 cases (26.4%) where mothers were pregnant for 40-42 days; 32 cases (60.4%) where mothers were pregnant for 45-83 days; and 7 cases (13.2%) where mothers were pregnant for 84-112 days. In this group, 20.7% (11/53) of the fathers were HBsAg-positive and simultaneously receiving ETV antiviral therapy. In the control group, 59 couples and infants were eligible and enrolled in the control group; that is, they were receiving long-term TDF anti-viral therapy. Among them, there were 17 cases (28.8%) where mothers were pregnant for 40-42 days; 37 cases (62.7%) where mothers were pregnant for 44-82 days; and 5 cases (8.5%) where mothers were pregnant for 85-111 days. In this group, HBsAg-positive fathers accounted for 25.4% (15/59) and simultaneously receivedETV antiviral therapy. All mothers in both groups had a common characteristic of irregular menstruation or menstrual disorder. In total, they had 54 newborns in the observational group (one twin), and 59 newborns in the control group; 9 mothers were excluded in the observational group, the remaining 44 couples and 45 infants completed the study, and 8 mothers were excluded in the control group, the remaining 51 couples and 51 infants completed the study, primarily due to incomplete data or loss of follow-up (Fig. 1).

Between the two groups, there were no significant differences in the maternal and paternal age, height, weight, or gravidity (P>0.05). In both groups, the fathers' HBV DNA loads were detected to be <500 IU/ml at delivery. In the observational group, the mothers' HBV DNA loads were <500 IU/ml at delivery in the observational group. In the control group, the mothers' HBV DNA loads were 3.17±0.83 IU/ml. The characteristics at baseline of the couples and infants in the two groups are shown in Table I.

Safety evaluation of mothers. ETV was initiated in mothers with CHB mothers in the observational group. After an accidental pregnancy, ETV was replaced with TDF immediately. TDF was initiated in the mothers with CHB in the control group, and after an accidental pregnancy, patients continued to receive TDF. After delivery, all mothers in the two groups continued antiviral therapy and breastfed their newborns. The gestational weeks, used as an indicator of fetal development in the study, were similar between the two groups, 39.31±1.22 vs. 39.52±1.35 weeks (P>0.05; Table I). During the study period, there were no instances of drug discontinuation due to any severe adverse events. The incidence of pregnancy complications did not differ significantly between the two mothers (Table II). No significant change in serum creatinine levelswas observed between baseline and 28 weeks postpartum (P>0.05). However, there was a significant decrease in the mean estimated glomerular filtration rate and the serum phosphorous levels from baseline to 28 weeks postpartum (P=0.0348 and P=0.0418, respectively; Table III) in the observational group. Urine analysis was performed in the two groups. Urine protein or urine blood was observed between the baseline and 28 weeks postpartum, and a significant difference was observed between the groups, with a lower value in the observational group (P=0.018 and P=0.005, respectively; Table III).

Safety evaluation of infants. Among the 96 infants enrolled, there were no significant differences in length, weight, head

Table I. Clinicopathological characteristics of the mothers, fathers, and infants in both groups.

A, Maternal characteristics

Variable	Observation	Control	χ^2, t-value	P-value
Age, year[a]	24±2.1	25±2.2	2.256	0.3781
Height, cm[a]	161±5.2	159±5.6	1.794	0.3091
Weight, kg[a]	56±5.2	54±5.8	1.758	0.2306
Gravidity, n	2±1.0	2±1.0	0.000	0.4971
HBV DNA levels at delivery IU/ml[a]	<500	3.17±0.83		
Abnormal urinanalysis, n[b]	0/44	0/51		
Creatinine, mmol/l[a]	58.44±12.91	60.21±14.12	0.634	0.273
eGFR, ml/min/1.73 m^2[a]	126.41±12.23	124.99±12.01	0.570	0.4478
Serum phosphate, mg/dl[a]	3.53±0.69	3.67±0.71	0.971	0.4254

B, Paternal characteristics

Variable	Observation	Control	χ^2, t-value	P-value
Age, year[a]	26±2.1	26±2.2	0.000	0.3781
Height, cm[a]	178±5.3	176±6.3	1.659	0.1217
Weight, kg[a]	69±5.1	64±5.2	4.715	0.4501
HBV DNA levels at delivery IU/ml	<500	<500		

C, Infant characteristics at birth

Variable	Observation	Control	χ^2, t-value	P-value
Week of pregnancy at birth[a]	39.31±1.22	39.52±1.35	0.790	0.2474
Preterm infants, n	2/45	1/51	0.487	0.912
Weight, kg[a]	3.42±0.33	3.34±0.31	0.066	0.3317
Height, cm[a]	49.82±1.58	49.45±1.52	1.162	0.3928
Head circumference, cm[a]	33.2±3.6	33.5±3.4	0.417	0.3452
Sex, Male/female, n	24/21	26/25	0.053	0.818
1 min Apgar score[a]	9.86±0.53	9.78±0.51	0.749	0.3934
8 min Apgar score[a]	9.78±0.59	9.81±0.55	0.256	0.3128
Jaundice, n	5	7	0.119	0.730
Other internal and surgical diseases, n	0	0		
Delivery mode, cesarean/head, n	23/21	24/27	0.257	0.612

[a]Mean ± SD. [b]Consisting of urine protein or urine blood. HBV, Hepatitis B virus; eGFR, estimated glomerular filtration rate.

circumference, and 1 and 8-min Apgar scores between the newborns, or the rates of cesarean section (Table I). The incidence of adverse events in infants was similar between the two groups, and the congenital disability rate was also similar (P>0.05; Table IV). In addition, during the 28, 48, and 96-week postpartum follow-up period, no abnormal signs or symptoms were reported among the infants. The physical parameters stratified by the sex of infants were within normal ranges compared with the national children's reference values (20). The specific data comparisons between the physical growth parameters of infants with or without ETV exposure and the national standards for infant growth are presented in Table V.

Efficacy mothers and infants in the two groups. At delivery, all mothers had an HBV DNA viral load of <500 IU/ml (less than the detection limit) in the observational group, and the HBV DNA viral load was 3.17±0.83 (SD) in the control group. HBV DNA viral load was <500 IU/ml (less than the detection limit) in two all fathers in both groups (Table I).

All newborns had HBV DNA viral loads <500 IU/ml at birth in the two groups, but 9 newborns were HBsAg-positive (19.6%, 9/46) in the observational group, and 11 newborns were HBsAg-positive (21.2%, 11/52) in the control group. All infants enrolled in the study received appropriate passive-active immunoprophylaxis. At 24-28 weeks, all infants became HBsAg negative and anti-HBs positive in both groups (Table VI).

Table II. Maternal adverse events and complications in the two groups.

A, Maternal adverse events

Adverse events or complications, n	Observation, n=44	Control, n=51	χ^2	P-value
Fatigue	1	2	0.210	1.000
Headache	0	0		
Constipation	2	2	0.023	1.000
Diarrhea	0	0		
Nausea	0	1	0.872	1.000
Vomiting	0	0		
Pruritus	0	0		
Skin rash	1	1	0.011	1.000
Insomnia	2	3	0.085	1.000
Dizziness	1	1	0.011	1.000
Abdominal pain	0	0		
Jaundice	0	0		
Arrhythmia	0	0		
CK elevation	0	0		
Hepatitis flare	0	0		

B, Maternal complications

Adverse events or complications, n	Observation, n=44	Control, n=51	χ^2	P-value
Hyperemesis gravidarum	1	0	1.171	0.941
Gestational hypertension	3	0	3.591	0.191
Placenta previa	2	0	2.368	0.411
Fetal growth retardation	1	1	0.011	1.000
Intrahepatic cholestasis of pregnancy	3	2	0.397	0.865
Membrane prerupture	4	5	0.014	1.000
Preterm delivery	2	1	0.516	0.897
Gestational diabetes mellitus	1	2	0.210	1.000
Postpartum hemorrhage	2	2	0.023	1.000
Fetal loss or stillbirth	0	0		
Preeclampsia	0	1	0.872	1.000
Oligohydramnios	0	0		
Threatened abortion	0	0		
Polyhydramnios	0	0		
Induced labor	0	0		

Discussion

ETV is recommended for general use as a first-line therapy for patients with CHB (10-14). Accidental pregnancies occurred in our clinical practice whilst the couples were receiving long-term ETV antiviral medication. All mothers in the present study exhibited irregular menstruation or menstrual disorder. To the best of our knowledge, there have been few related studies.

This study used ETV in mothers' early-middle stages of accident pregnancy in the observational group, and TDF was replaced with ETV for the first time according to the guidelines (10-13). Additionally, 11 couples co-infected with HBV began ETV antiviral medication concurrently with an unintended pregnancy.

While being chosen, control women continued to receive TDF antiviral medication according to the guidelines, which they had started in the early-mid stages of their accident pregnancy (10-13). Additionally, 15 couples co-infected with HBV had unintentional pregnancies while beginning ETV antiviral medication simultaneously.

With or without exposure to ETV in the first and second trimesters, the aim of the present study was to the monitor safety of the mothers and their offspring. The results showed that from the time of delivery (birth) to the 28, 48, and 96-week follow-up periods, ETV exposure during pregnancy seemed to be safe for mothers and infants. No congenital flaws or aberrant physical developments were discovered in the newborns exposed to ETV. In the current trial, there was a 100% success

Table III. Maternal urine, renal function, and serum phosphate levels.

A, Observation group

Variable	Baseline	28 weeks postpartum, n=44	P-value
Urinalysis abnormal, n[d]	0/44	7/44	0.018[a]
Creatinine, mmol/l[b]	58.44±12.91	60.01±11.99	0.3130
eGFR, ml/min/1.73 m^{2c}	126.41±12.23	119.45±16.13	0.0348
Serum phosphate, mg/dl[c]	3.53±0.69	3.31±0.53	0.0418

B, Control group

Variable	Baseline	28 weeks postpartum, n=51	P-value
Urinalysis abnormal, n[d]	0/51	9/51	0.005[b]
Creatinine, mmol/l[c]	60.21±14.12	59.84±11.45	0.0689
eGFR, ml/min/1.73 m^{2c}	124.99±12.01	121.01±14.98	0.0589
Serum phosphate, mg/dl[c]	3.67±0.71	3.42±0.59	0.0948

[a]P<0.05, [b]P<0.01. [c]Mean ± SD. [d]Consisting of urine protein or urine blood. eGFR, estimated glomerular filtration rate.

Table IV. Birth defects, malformations, and adverse events.

Defects, adverse events, n	Observation, n=45	Control, n=51	χ^2	P-value
Fetal distress	0	0		
Umbilical hernia	0	0		
Asphyxia	0	1	0.892	1.000
Hemolysis disease of newborn	1	2	0.228	1.000
Skin rash	1	2	0.228	1.000
Diarrhea	3	4	0.049	1.000
Vomiting	2	1	0.487	0.912
Low birth weight	2	1	0.487	0.912
Neonatal jaundice	5	7	0.119	0.730
Macrosomia	0	0		
Bronchitis	0	1	0.892	1.000

rate in preventing mother-to-child transmission of HBV when combined with routine HBV immunoprophylaxis for babies. TDF was also well tolerated during pregnancy, and no significant safety issues for mothers or babies were recorded.

In summary, the present study supports using ETV or TDF in the first and second trimesters of a pregnancy. That is, accidental pregnancies for mothers with CHB treated with ETV in the first and second trimesters do not need to be terminated. No obvious association of human teratogenicity with exposure to ETV was reported in fetuses during pregnancy (21). However, previous studies have reported inconsistent results to the present study. Comprehensive genetic studies identified the genotoxic potential of ETV and suggested that single-strand breaks and post-replication repair pathways may inhibit ETV-induced genotoxicity (22). According to the US Antiretroviral Registration Website (23), as of January 2013, newborn defect rates were 3.64% (2/55) for 55 mothers who started ETV antiviral medication during the first three months of pregnancy.

However, other studies have shown similar results; it was safe for fathers with CHB during exposure to ETV pregnancy and the baby had no abnormalities or deformities (24-27); there was no need to terminate the pregnancy.

In the present study, after delivery, all mothers in the two groups continued TDF antiviral therapy and breastfed their offspring. During the follow-up period of 96 weeks postpartum, no abnormal signs or symptoms were reported among the infants. The infants' physical characteristics, stratified by sex, were within the normal range compared to the national reference values for children (20). Previous studies on mothers with CHB treated with TDFdetermined that it was ok for them to breastfeed (28,29).

Furthermore, no congenital flaws were observed in mothers and fathers co-infected with HBV. According to a previous study, HBsAg positivity in couples had no appreciable impact on

Table V. Growth parameters of infants with or without ETV exposure.

Growth Parameters	National standard, n=3,811	Observation, n=45	Control, n=51	P-value	
				Observation vs. National standard	Observation vs. Control
At birth					
Male height, cm	50.4±1.6	49.6±1.59	50.1±1.58	0.5041	0.4803
Male weight, kg	3.38±0.4	3.40±0.41	3.39±0.39	0.3807	0.3630
Male head circumference, cm	34.0±1.4	33.9±1.38	34.1±1.39	0.4738	0.4826
Female height, cm	49.8±1.6	49.9±1.57	50.1±1.59	0.4570	0.4677
Female weight, kg	3.26±0.4	3.35±0.35	3.29±0.31	0.1279	0.1999
Female head circumference, cm	33.7±1.3	33.9±1.2	34.0±1.24	0.2528	0.4132
After 28 weeks					
Male height, cm	69.5±2.3	70.1±2.3	69.7±2.2	0.5275	0.3775
Male weight, kg	8.68±0.94	8.73±0.93	8.71±0.94	0.4875	0.4731
Male head circumference, cm	43.8±1.3	43.7±1.29	40.1±1.31	0.4986	0.4603
Female height, cm	67.9±2.3	68.1±2.4	67.4±2.31	0.3172	0.3939
Female weight, kg	8.03±0.9	7.99±0.85	8.01±0.87	0.3230	0.4389
Female head circumference, cm	42.6±1.2	42.9±1.21	43.0±1.22	0.4414	0.4798
After 48 weeks					
Male height, cm	77.6±2.7	78.1±2.75	77.9±2.71	0.4040	0.4574
Male weight, kg	10.26±1.10	10.67±1.09	10.98±1.11	0.4934	0.4526
Male head circumference, cm	46.3±1.3	46.9±1.31	47.0±1.31	0.4438	0.4976
Female height, cm	76.2±2.7	76.9±2.71	77.0±2.71	0.4586	0.4976
Female weight, kg	9.65±1.06	9.87±1.09	9.76±1.05	0.3690	0.3961
Female head circumference, cm	45.3±1.3	46.1±1.26	46.8±1.31	0.4120	0.3960
After 96 weeks					
Male height, cm	90.6±3.6	89.9±3.51	90.4±3.6	0.4335	0.4333
Male weight, kg	12.98±1.48	12.0±1.35	12.31±1.31	0.2202	0.4156
Male head circumference, cm	48.5±1.4	49.0±1.51	48.9±1.49	0.2120	0.4611
Female height, cm	89.3±3.6	89.1±3.49	90.1±3.61	0.4128	0.4105
Female weight, kg	12.36±1.41	12.56±1.41	12.99±1.43	0.5275	0.4638
Female head circumference, cm	47.5±1.4	49.8±1.42	47.9±1.4	0.4194	0.4587

Table VI. Efficacy of the anti-viral treatments on the infants.

Status	Observation, n=45	Control, n=51	χ^2	P-value
HBV at birth				
HBV DNA positive	0/45	0/51		
HBsAg positive	9/45	11/51	0.036	0.850
HBV at 24-28 weeks				
HBV DNA positive	0/45	0/51		
HBsAg positive	0/45	0/51		
Anti-HB positive	45/45	51/51		

HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; anti-HB, antibody against HBsAg.

fetal development, pregnancy outcomes, or on the mother's and newborn's health (30). In addition, during TDF antiviral medication, maternal urine analysis, renal function, and serum phosphate should be observed, as TDF may have bone and kidney toxicity.

The present study has some limitations. First, this was a single-center study. Second, the follow-up duration in the current study was 96 weeks. Infants exposed to TDF or ETV have not been studied with regard to long-term effects. Hence,

additional multicenter studies with larger sample sizes and longer follow-up times are required to demonstrate the effectiveness and safety. Moreover, only early-middle pregnancy was considered regarding the safety statistics of ETV. Given that the ethics of the present study cannot be upheld, as ETV is classified as FDA Pregnancy Category C, pregnant women may not be affected by ETV. As a result, only mothers who started ETV during an early-mid pregnancy were included.

In conclusion, starting ETV or TDF in the early or middle stages of pregnancy is safe for mothers and their unborn children. Important data from the present study suggest using TDF therapy instead of ETV for the mother in the early to middle stages of an accidental pregnancy and there is no need to terminate a pregnancy.

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Availability of data and materials

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

Authors' contributions

LC, SL, and HZ designed the study. JD performed the experiments. JW, QY, LD, and YG collected and analyzed the data. XX analyzed the data and guided the study. LC and SL wrote the manuscript. LC and SL confirm the authenticity of all the raw data All authors have read and approved the final manuscript.

Ethics approval

The Qinhuangdao Third Hospital Ethical Committee approved the present study (approval no. QHDSDSYYEC-3). The need for informed consent was waived. The current study complied with the Declaration of Helsinki.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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