Received: 23 July 2021 | Revised: 15 April 2022 | Accepted: 24 June 2022

DOI: 10.1111/liv.15349

Liver INTERNATIONAL WILEY

ORIGINAL ARTICLE

Impact of in vitro fertilization-embryo transfer on mother-to-infant transmission in women with chronic HBV infection

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Funding information
Beijing Science and Technology Commission Research Project, Grant/Award Number: D161100002716002; Digestive Medical Coordinated Development Center of Beijing Hospitals Authority, Grant/Award Number: XXT28 and XXZ0302; Beijing Municipal Science & Technology Commission, Grant/Award Number: Z151100004015122; National Science and Technology Major Project of China, Grant/Award Number: 2018ZX10715-005-003-005, 2017ZX10201201-002-006 and 2017ZX10201201-001-006; Beijing Hospitals Authority Clinical medicine Development of special funding support, Grant/Award Number: XMLX 202127 and XMLX 201706

Handling Editor: Alessio Aghemo

Abstract

Background and Aims: In vitro fertilization-embryo transfer (IVF-ET) may increase the risk of mother-to-child transmission (MTCT) of hepatitis B virus (HBV). The purpose of this study was to investigate the impact and safety of IVF-ET on MTCT in women with chronic HBV infection (CHB).

Methods: The data of 298 women who got pregnant by IVF-ET and their 375 children were collected retrospectively. Mothers were divided into the CHB group ($n = 224$) and the control group (HBsAg negative, $n = 74$). After birth, newborns were routinely vaccinated with the hepatitis B vaccine, and infants in the CHB group were injected with hepatitis B immunoglobulin within 2 h after birth. Demographic information, clinical data and laboratory test results were collected. The primary outcome measures were the MTCT rate of HBV, and the secondary outcome measures were the safety of the mother and infant.

Results: There was no case of HBV MTCT in all 282 newborns born in the CHB group and 93 neonates born in the control group. Of the two groups, the birth weight (3056.74 ± 601.65 vs. 2926.24 ± 704.86, $P = .083$), length (49.22 ± 1.97 vs. 48.74 ± 3.09, $P = .167$), 5-min Apgar score (9.97 ± 0.21 vs. 9.90 ± 0.51, $P = .212$), days of pregnancy (265.70 ± 12.73 vs. 262.02 ± 17.50, $P = .064$) and neonatal malformation rate (0.71% vs. 0, $P = 1.000$) were similar. Two cases of neonatal malformation occurred in the CHB group. The incidences of pregnancy and childbirth complications were similar between the two groups.

Conclusion: IVF-ET does not increase the risk of MTCT in women with chronic HBV infection, and it is safe for mothers and infants.

Abbreviations: ALT, alanine aminotransferase; cccDNA, covalently closed circular DNA; CHB, chronic HBV infection; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IVF-ET, in vitro fertilization-embryo transfer; MTCT, mother-to-child transmission.

KEYWORDS
hepatitis B virus infection, in vitro fertilization, infertility, IVF-ET, vertical transmission

1 | INTRODUCTION

Approximately 2 billion people worldwide are infected with the hepatitis B virus (HBV), and ~292 million people live with chronic infections.[1] An estimated 0.88 million people die of HBV infection-related liver failure, cirrhosis and primary hepatic cancer every year.[1] Mother-to-child transmission (MTCT) is the most important route for chronic HBV infection (CHB) in Asia.[2–4] In Chinese adults, 30–50% of chronic HBV infections are from MTCT.[5]

The median prevalence of infertility is about 9%,[6] and it's estimated that 48 to 186 million people globally suffer from infertility.[6–8] Studies have shown that a spouse with HBV infection will increase the incidence of tubal infertility.[9] In vitro fertilization-embryo transfer (IVF-ET) is an important method to treat infertility. In a reproductive centre in China, it was reported that 21.75% of couples who had in vitro fertilization were of chronic HBV infection.[10] However, it is not clear whether IVF-ET in mothers with chronic HBV infection will increase the risk of MTCT of HBV.

The main steps of IVF-ET include drug-induced ovulation, ultrasound-guided oocyte retrieval, fertilization of eggs and sperm in vitro culture medium, and implantation of fertilized eggs into the uterine cavity after 3–5 days of in vitro development. Oocyte retrieval and zygote implantation are invasive procedures, which theoretically may increase the risk of MTCT of HBV. Studies have shown that HBV can be detected in follicular fluid and even oocytes of HBV-infected women.[11–13] Previous studies have been focused on the impact of HBV infection on sperm quality, fertilized egg implantation rate, pregnancy rate, abortion rate and live birth rate.[11,14–19] Only one study with 41 chronic HBV-infected samples focused on infant HBV infection, in which there were 5 cases of HBeAg-positive and 18 infants born.[10] Although none of these infants was infected, the incidence of MTCT through IVF-ET treatment in chronic HBV-infected women remains to be determined. What's more, there is limited literature that focuses on the intrauterine development of HBV-infected women after successful IVF-ET. Therefore, we conducted a retrospective study to explore whether IVF-ET for HBV-infected mothers increases the risk of MTCT of HBV and affects intrauterine growth.

Lay summary

In this retrospective case-cohort study that included 298 mothers who got pregnant by IVF-ET and 375 infants delivered, no HBV mother-to-child transmission occurred in infants born to mothers with CHB. The intrauterine development indicators of infants born to CHB mothers were similar to those of infants born to HBsAg-negative mothers.

2 | MATERIAL AND METHODS

2.1 | Study design and population

This retrospective observational cohort study collected data from all CHB or non-CHB women who were pregnant with IVF-ET and delivered at Beijing Ditan Hospital from October 2010 to March 2019 and their newborns. CHB was defined as hepatitis B surface antigen (HBsAg) positive for more than 6 months with any status of Hepatitis B e antigen (HBeAg) and serum HBV DNA. The included cases should have complete medical records and laboratory results. Exclusion criteria: (1) Amniocentesis during pregnancy. (2) Pregnant women with syphilis, HIV, hepatitis C, TORCH series virus coinfection. (3) The couple's families had a history of the birth of congenital malformed foetuses. (4) Husband or wife suffered from neoplastic diseases. (5) Neonates born to women with CHB did not complete the hepatitis B vaccine and hepatitis B immune globulin (HBIG) vaccination after birth.

All eligible cases were divided into the CHB group and control group (non-CHB with negative HBsAg) according to their HBV infection status determined in the first trimester. IVF-ET are invasive procedures, which theoretically may increase the risk of MTCT of HBV even in mothers with negative or low HBV DNA levels, thus we enrolled all CHB women. CHB group was divided into the high viral load group (HBV DNA $\geq 2\times10^5$ IU/ml, 1 IU/ml = 5.82 copies/ml) and the low viral load group (HBV DNA negative and HBV DNA $<2\times10^5$ IU/ml) according to the level of HBV DNA tested in the first trimester. The high viral load group was further divided into the treated group and untreated group according to the use of antiviral drugs during pregnancy. All pregnant women had routine prenatal examination every 4 weeks before 28 weeks of pregnancy, and every 1–2 weeks after 28 weeks of pregnancy.

All pregnant women's medical information was collected from the health information system (HIS), lab information system (LIS) and patient survey, including the age of pregnant women, past medical history, pregnancy and delivery history, pregnancy complications, drug usage during pregnancy, all clinical biochemical and virological test results during pregnancy and delivery complications. Birth weight, height, Apgar score, neonatal screening results and hepatitis B test results 7–12 months after birth were collected from all newborns.

2.2 | Ethics approval

This study was approved by the Institutional Review Board of Beijing Ditan Hospital (no. JDLKZ2018D[012]-01), and informed consent

was exempted because of a retrospective study. The trial has been registered on ClinicalTrials.gov (ID: NCT03932851). All authors had access to the study data and approved the final manuscript.

2.3 | Prophylactic immunization of newborn

All neonates were injected with hepatitis B vaccine 10 μg (Dalian Hissen Biopharm Co., Dalian, China) within 2 h after birth. The 2nd dose was injected at 1 month and the 3rd dose at 6 months after birth. In addition, newborns born to CHB females were injected with hepatitis B immunoglobulin (HBIG) 100–200 IU (Chengdu Institute of Biological Products, Chengdu, China) within 2 h at birth. Heel blood samples were taken from all neonates 72 h after birth in the neonatal screening centre to detect congenital hypothyroidism and phenylketonuria. The auditory screening was done before the baby left the hospital. HBV serological and virological tests were taken in infants born to mothers with CHB during 1–6 months after finishing the third dose of the hepatitis B vaccine.

2.4 | Outcome measures

Negative HBsAg tested 7–12 months after birth was considered as a successful HBV MTCT prevention. Hepatitis B surface antibody (HBsAb) level ≥ 10 mIU/ml was considered positive and protective. The primary outcome measure was the rate of successfully preventing HBV MTCT. The secondary outcome measures were intrauterine growth of neonates, including length, weight, 5-min Apgar score and the incidence of adverse events during pregnancy and delivery.

2.5 | Statistical analysis

For continuous data of normal distribution, variables were expressed as mean ± standard deviations, and a *t*-test was used for comparison between groups. Continuous data for skewness distribution, variables were expressed by medians and interquartile ranges (Q1, Q3), and comparisons between groups were nonparametric. The relation of two continuous variables was analysed by Spearman correlation. Categorical variables were expressed as frequencies and percentages, and the Chi-squared test or Kruskal–Wallis test was used to compare these data. All statistical tests were two-sided, and *P* values <.05 was considered statistically significant. For all analyses, SPSS software (version 25.0) was used.

3 | RESULTS

3.1 | Enrollment and clinical characteristics of pregnant women

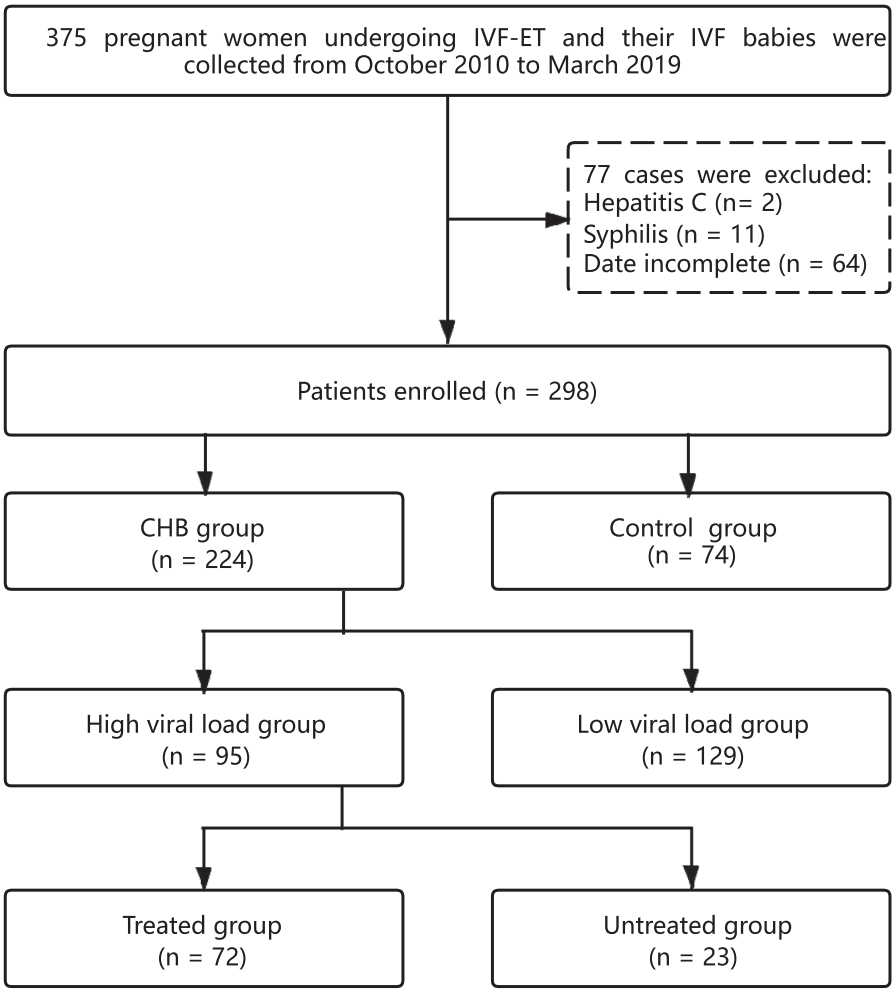
There were 375 women who received IVF-ET and delivered in Beijing Ditan Hospital between October 2010 and March 2019. Seventy-seven cases were excluded, including 2 cases infected with hepatitis C, 11 cases infected with syphilis and 64 due to incomplete data (all in the CHB group without infant's data of HBV biomarkers test during follow-up). Two hundred and ninety-eight pregnant women, 224 in the CHB group and 74 in the control group, aged from 25 to 51 years old (35.65 ± 4.38 years) were enrolled in this study. There were fewer cases in the control group, mainly because the Department of Obstetrics and Gynaecology of Beijing Ditan Hospital is good at preventing mother-to-child transmission of hepatitis B, so many CHB pregnant women choose to give birth here.

In the CHB group, there were 107 women with positive HBeAg and 117 with negative HBeAg at baseline (in the first trimester). The rates of positive HBeAg in the high viral load group and treated group were significantly higher than those in the low viral load group and the untreated group (90.53% vs. 16.28%, $P = .000$ and 94.44% vs. 78.26%, $P = .021$). 151 (67.41%) women were serum HBV DNA positive with a mean HBV DNA level of $5.95 \pm 2.26 \log_{10}$ IU/ml, in which 42.41% (95/224) patients with HBV DNA $\geq 2.0 \times 10^5$ IU/ml (High viral load group) and 57.58% (129/224) patients with HBV DNA $< 2.0 \times 10^5$ IU/ml (Low viral load group). In the CHB group, no women took antiviral drugs before IVF-ET, whilst 75.78% (72/95) of patients with high viral load received antiviral drugs during the third-trimester pregnancy (treated group), including Lamivudine in 12 cases, Telbivudine in 54 cases, and Tenofovir in 6 cases. 24.21% (23/95) were not treated with any antiviral drug (untreated group) (Figure 1). In the control group, 35 females had positive and protective HBsAb (HBsAb≥10 mIU/ml), 36 females had negative and unprotective HBsAb (HBsAb<10 mIU/ml), and 3 females' HBsAb levels were unknown.

There was no significant difference in maternal age, gravidity, parity, days of pregnancy, or rate of paternal HBV infection between the CHB group and control group ($P > .05$), but the baseline alanine aminotransferase (ALT) level in the CHB group was significantly higher than that in control [23.90 (17.05, 33.40) vs. 16.25 (11.88, 26.75), $P = .044$]. In the CHB group, the maternal age, gravidity, parity, gestational week of delivery and paternal infection rate in the high viral load group were similar to those in the low viral load group ($P > .05$), but the high viral load group had significantly higher ALT level than the low viral load group [28.40 (21.60, 41.85) vs. 21.40 (14.70, 28.08), $P = .001$]. Before delivery, there were 140 (62.50%) cases being HBV DNA positive with a level of 4.41 ± 1.78 log IU/ml in the CHB group (Table 1).

3.2 | Pregnancy and childbirth complications

The twinning rate was 26.33% in the CHB group and which was 24.32% in the control group ($P = .731$). The control group had a higher incidence of gestational diabetes mellitus (60.81% vs. 46.43%, $P = .032$), gestational hypertension (13.51% vs. 5.36%, $P = .020$) and premature rupture of membranes (25.68% vs. 14.73, $P = .032$) than the CHB group, whilst the incidence of other complications, including hypothyroidism, intrahepatic cholestasis of pregnancy, placenta



CHB: Chronic HBV infection
IVF-ET: In vitro fertilization-embryo transfer
High viral load: HBV DNA HBV DNA ≥ 2×10^5 IU/mL
Low viral load: HBV DNA HBV DNA < 2×10^5 IU/mL

FIGURE 1 Enrollment of the trial participants. CHB, Chronic HBV infection; IVF-ET, In vitro fertilization-embryo transfer. High viral load: HBV DNA HBV DNA ≥2×10^5 IU/ml. Low viral load: HBV DNA HBV DNA <2×10^5 IU/ml.

previa, abruptio placentae, third-degree amniotic fluid contamination, polyhydramnios, oligohydramnios, preterm birth, and postpartum haemorrhage were similar between the two groups (Table 2). Amongst the pregnant women in the CHB group, the incidence of thyroid diseases in the low viral load group was significantly higher than that in the high viral load group (5.43% vs. 0, $P = .022$). All mothers stopped antiviral treatment after delivery in the treated group.

3.3 | Neonatal development and prevention of MTCT of HBV

Amongst the 298 pregnant women, there were 77 twin pregnancies and 375 newborns delivered, including 204 males and 171 females, with a length of 49.10 ± 2.30 cm, a weight of 3024.37 ± 630.37 g and a 5-min Apgar score of 9.95 ± 0.31. Congenital hypothyroidism, phenylketonuria or hearing abnormality were not found in all children. There were 2 cases of neonatal malformation (1 neonatal left ear appendage and 1 neonatal congenital heart malformation) in the low viral load group without using antiviral drugs.

At birth, there was no significant difference in birth weight, length, 5-minute Apgar score, days of pregnancy, the percentage of male newborns or neonatal malformation rate between CHB and control group, The rate of successfully HBV MTCT prevention in the CHB group was 100%. (Table 3).

In the CHB group, HBV DNA was undetectable in all infants, but 35 infants had positive HBsAg with levels between 0.05 and 0.19 mIU/ml, the rate of positive HBsAg in the high viral load group was significantly higher than that in the low viral load group (17.70% vs. 8.88%, $P = .020$), and there was no significant difference of infants' birth weight, length, 5-minute Apgar score, days of pregnancy, neonatal malformation rate between the two groups ($P > .05$). In the treated group, the percentage of male neonates was significantly higher than that of the untreated group (73.07% vs. 47.13%, $P = .020$). However, there were no significant differences in birth weight, height, 5-minute Apgar score, days of pregnancy and

TABLE 1 Baseline characteristics of the subjects

Values	CHB group ($n = 224$)	Control group ($n = 74$)	*P*-value	High viral load group ($n = 95$)	Low viral load group ($n = 129$)	*P*-value	Treated group ($n = 72$)	Untreated group ($n = 23$)	*P*-value
Age (year, mean ± *SD*)	35.64 ± 4.27	35.68 ± 4.74	.950	35.09 ± 4.47	36.04 ± 4.09	.102	35.08 ± 4.50	35.13 ± 4.48	.965
No. pregnancies (mean ± *SD*)	1.78 ± 0.93	2.11 ± 1.33	.050	1.76 ± 1.01	1.79 ± 0.88	.796	1.83 ± 1.09	1.52 ± 0.67	.198
No. deliveries (mean ± *SD*)	1.06 ± 0.26	1.15 ± 0.39	.082	1.03 ± 0.23	1.09 ± 0.28	.116	1.03 ± 0.24	1.04 ± 0.21	.776
Gestational weeks (days, mean ± *SD*)	268.25 ± 12.17	264.66 ± 17.53	.105	267.65 ± 13.17	268.69 ± 11.40	.529	267.89 ± 12.40	266.91 ± 15.61	.759
Husband HBV infection (%)	11 (4.91)	4(5.41)	1.000	3 (3.16)	8 (6.2)	.362	3 (4.17)	0 (0.00)	1.000
ALT level [U/L, median (Q1, Q3)]	23.90 (17.05, 33.40)	16.25(11.88, 26.75)	.044	28.40 (21.60, 41.85)	21.40 (14.70, 28.08)	.001	28.45 (21.60, 41.30)	28.00 (19.63, 54.28)	.781
HBeAg positive (%)	107 (47.32)	–	–	86 (90.53)	21 (16.28)	.000	68 (94.44)	18 (78.26)	.021
HBV DNA (log_{10} IU/MI, mean ± *SD*)	5.95 ± 2.26[a]	–	–	7.26 ± 1.86	1.61 ± 1.84[a]	.000	7.16 ± 2.05	7.57 ± 0.93	.380

Note: Values are presented as *n* (%), means ± standard deviations, or medians (Q1, Q3).

Abbreviation: ALT, Alanine aminotransferase.

[a]Only include HBV DNA positive.

TABLE 2 Complications during pregnancy and delivery

Values	CHB group ($n = 224$)	Control group ($n = 74$)	*P*-value	High viral load group ($n = 95$)	Low viral load group ($n = 129$)	*P*-value	Treated group ($n = 72$)	Untreated group ($n = 23$)	*P*-value
Diabetes (%)	104 (46.43)	45 (60.81)	.032*	39 (41.05)	65 (50.39)	.166	30 (41.67)	9 (39.13)	.830
Hypothyroidism (%)	7 (3.13)	5 (6.76)	.180	0 (0.00)	7 (5.43)	.022*	0 (0.00)	0 (0.00)	1.000
Intrahepatic cholestasis of pregnancy (%)	11 (4.91)	1 (1.35)	.306	5 (5.26)	6 (4.65)	.834	4 (5.56)	1 (4.35)	1.000
Hypertension disorder of pregnancy (%)	12 (5.36)	10 (13.51)	.020*	6 (6.32)	6 (4.65)	.585	4 (5.56)	2 (8.70)	.630
Placenta previa (%)	2 (0.89)	3 (4.05)	.100	0 (0.00)	2 (1.55)	.509	0 (0.00)	0 (0.00)	1.000
Placental abruption (%)	2 (0.89)	0 (0.00)	1.000	0 (0.00)	2 (1.55)	.509	0 (0.00)	0 (0.00)	1.000
Meconium staining of the amniotic fluid (%)	7 (3.13)	0 (0.00)	.199	4 (4.21)	3 (2.33)	.461	2 (2.78)	2 (8.70)	.246
Polyhydramnios (%)	2 (0.89)	0 (0.00)	1.000	1 (1.05)	1 (0.78)	1.000	1 (1.39)	0 (0.00)	1.000
Oligohydramnios (%)	8 (3.57)	5 (6.76)	.321	2 (2.11)	6 (4.65)	.472	2 (2.78)	0 (0.00)	1.000
Preterm birth (%)	40 (17.86)	17 (22.97)	.332	21 (22.11)	19 (14.73)	.154	16 (22.22)	5 (21.74)	.961
Twin pregnancy (%)	59 (26.33)	18 (24.32)	.731	26 (27.36)	33 (25.58)	.764	21 (29.16)	5 (21.73)	.487
Postpartum haemorrhage (%)	36 (16.07)	14 (18.92)	.570	18 (18.95)	18 (13.95)	.315	12 (16.67)	6 (26.09)	.363
Premature rupture of membranes (%)	33 (14.73)	19 (25.68)	.032*	12 (12.63)	21 (16.28)	.447	9 (12.5)	3 (13.04)	1.000

*$P < .05$.

TABLE 3 Characteristics of newborns and MTCT rate of HBV

Characteristic	CHB group ($n = 282$)	Control group ($n = 93$)	*P*-value	High viral load group ($n = 113$)	Low viral load group ($n = 169$)	*P*-value	Treated group ($n = 87$)	Untreated group ($n = 26$)	*P*-value
Length (cm, m, mean ± *SD*)	49.22 ± 1.97	48.74 ± 3.09	.167	49.41 ± 1.55	49.09 ± 2.20	.156	49.47 ± 1.22	49.19 ± 2.37	.567
Weight (g, mean ± *SD*)	3056.74 ± 601.65	2926.24 ± 704.86	.083	3071.68 ± 546.78	3046.75 ± 637.10	.726	3052.87 ± 526.20	3134.62 ± 617.70	.506
Apgar score at 5 min (mean ± *SD*)	9.97 ± 0.21	9.90 ± 0.51	.212	9.97 ± 0.16	9.97 ± 0.23	.903	9.99 ± 0.11	9.92 ± 0.27	.240
Male (%)	148 (52.48)	56(60.22)	.194	60 (54.54)	88 (52.07)	.866	41 (47.13)	19 (73.07)	.020*
Gestational days (days, mean ± *SD*)	265.70 ± 12.73	262.02 ± 17.50	.064	266.64 ± 12.37	265.08 ± 12.96	.314	266.94 ± 11.85	265.62 ± 14.19	.633
Neonatal malformation (%)	2 (0.71)	0 (0.00)	1.000	0 (0.00)	2 (1.18)	.246	0 (0.00)	0 (0.00)	1.000
HBsAg (+) at birth (%)	35 (12.41)	-	-	20 (17.70)	15 (8.88)	.028*	13 (14.94)	7 (26.92)	.160
HBV DNA (+) at birth (%)	2 (0.71)	-	-	0 (0.00)	2 (1.18)	.518	0 (0.00)	0 (0.00)	-
HBsAg (−) after 7 month (%)	282 (100%)	-	-	113 (100%)	169 (100%)	-	87 (100%)	26 (100%)	-

*$P < .05$.

neonatal malformation rate between the two groups. All 282 neonates were born to women with CHB-produced protective antibodies (anti-HBs ≥10 mIU/ml), with a median anti-HBs level of 258.02 (12.57, 1000) mIU/ml.

4 | DISCUSSION

With the increasing incidence of infertility, more and more HBV-infected couples need to use IVF-ET to achieve the purpose of fertility. It is reported that HBV infection in men can affect sperm quality,[15,20] resulting in lower fertilization rates during IVF-ET and possibly HBV of paternal-fetal transmission.[14–16] In this study, the rates of husband with HBV infection were of no difference between the CHB group and control group, and even between each subgroup of the chronic HBV infection group, excluding the impact of male HBV infection on the outcome of the study. Women undergoing IVF-ET are a special group who are generally old and accompanied by infertility as well as other diseases. Therefore, we selected normal women who underwent IVF-ET as the control group in this study, rather than CHB women who did not undergo IVF-ET.

The main modes of HBV transmission are blood transmission, MTCT and sexual transmission.[21] China's Guidelines for the Prevention and Treatment of Chronic Hepatitis B (2010, 2015 and 2019 edition)[22–24] recommend that for newborns of HBsAg-positive mothers, 100 IU hepatitis B immunoglobulin (HBIG) should be injected within 12 h after birth. Meanwhile, recombinant yeast-derived hepatitis B vaccine (10 μg) be inoculated at different sites of the body, and the second and the third dose of hepatitis B vaccine be administered at the age of 1 month and 6 months respectively. Despite timely prophylaxis, MTCT can still occur in 5%~15% of the infants born to mothers with high HBV DNA level.[25] Using antiviral medications in the third trimester could further reduce the MTCT rate to 0%,[26] indicating that HBV MTCT rarely happened in the first and second trimesters.

IVF is different from natural conception. IVF involves oocyte retrieval, in vitro fertilization, in vitro culture of fertilized eggs and implantation of fertilized eggs, which may cause oocyte-contaminated HBV in the first trimester. HBV DNA can be detected in IVF-ET oocytes, and the detection rate is related to the content of HBV DNA in female blood.[12] It has also been found that the presence of HBV cccDNA and HBV DNA in the ovary was significantly associated with increased HBV intrauterine infection.[27] Therefore, it was hypothesized that IVF-ET in women with chronic HBV infection may increase the risk of mother-to-child transmission of HBV. In this study, a retrospective cohort study was conducted to investigate whether IVF-ET increases the risk of HBV mother-to-child transmission in women with chronic HBV infection. The results showed that all newborns born to women with chronic HBV infection undergoing IVF-ET, even those with high HBV viral load, could be effectively protected from the MTCT of HBV by timely injection of HBIG combined with hepatitis B vaccine after birth. The results indicate that IVF did not increase the risk of MTCT of HBV in pregnant women with chronic HBV infection based on prophylactic immunization.

It is unclear why IVF-ET did not increase the risk of MTCT of HBV in pregnant women with chronic HBV infection in our study. Even in women with high HBV viral load, HBV DNA can be detected in only 9.6% of oocytes,[12] and other studies have shown that HBV infection in oocytes and embryos can lead to a decrease in implantation rate.[17,18] It should be speculated that a small number of HBV-infected oocytes often fail to successfully implant into the uterine cavity, or fail to develop a mature fetus. The fetus that can mature may be the oocytes and embryo cells that are not infected by the HBV virus. Since our hospital cannot perform IVF-ET, it is regrettable that the success rate of IVF in the CHB group and control group could not be demonstrated in this study and we cannot confirm our speculation.

In this study, there were 12.41% (35/282) neonates born to CHB mothers and 17.70% (20/113) neonates born to CHB mothers with high HBV viral load were serum HBsAg positive at birth, and all the neonates did not develop HBV infection in the follow-up. Previous studies reported in CHB mothers with high HBV viral load and did not receive antiviral treatment in pregnancy, there were 29.79% of infants with HBsAg positive at birth and 8% of infants developed HBV infected in the follow-up, and those were 10% and 0% in infants born to women with high viral load taking the antiviral drug during pregnancy.[28] It is suggested that HBsAg positive at birth does not indicate neonatal infection. In the present study, all children produced protective antibodies in follow-up, suggesting that IV-ET does not affect the production of hepatitis B surface antibodies.

The results of our study showed that the incidences of pregnancy and childbirth complications, including hypothyroidism, intrahepatic cholestasis of pregnancy, placenta previa, placental abruption, polyhydramnios, oligohydramnios, premature delivery, postpartum haemorrhage and congenital phenylketonuria were similar between CHB group and control group, whilst the rates of diabetes, pregnancy-induced hypertension and premature rupture of membranes were lower in the CHB group. The birth weight, length, Apgar score, incidence of birth deformity, congenital phenylketonuria, congenital hypothyroidism and congenital deafness were similar between the two groups. It is indicated that the risk of complications during pregnancy and delivery does not increase after successful IVF-ET in HBV-infected women, and the intrauterine growth of the foetus is not affected.

To sum up, the results of this study indicate that IVF did not increase the risk of MTCT of HBV or affect the intrauterine development of the fetus in women with chronic HBV infection. HBV-positive patients who underwent IVF do not appear to have an increased risk of pregnancy-related complications although the non-pregnancy cohort was relatively small.

FUNDING INFORMATION

This study was funded by the Beijing Hospitals Authority Clinical medicine Development of special funding support (grant no. XMLX 201706 and XMLX 202127), National Science and Technology Major Project of China (grant no. 2017ZX10201201-001-006, 2017ZX10201201-002-006 and 2018ZX10715-005-003-005), Beijing Municipal Science & Technology Commission (grant no. Z151100004015122), the Digestive Medical Coordinated Development Center of Beijing Hospitals Authority (grant no. XXZ0302 and XXT28), and Beijing Science and Technology Commission Research Project (grant no. D161100002716002).

CONFLICT OF INTEREST

Wei Yi, Minghui Li, Fangfang Sun, Huihui Lu, Zhan Zeng, Xiaoyue Bi, Liu Yang, Yanjie Lin, Xiuzhen Cao, Yuhong Hu, Mingfang Zhou, Lu Zhang, Yao Lu, Gang Wan and Yao Xie declare that there is no conflict of interest.

ETHICS APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Institutional Review Board of Beijing Ditan Hospital (no. JDLKZ2018D [012]-01).

CLINICAL TRIAL NUMBER

ClinicalTrials.gov (ID: NCT03932851).

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REFERENCES

1. World Health Organization. Hepatitis B. Fact Sheet. Available at: http://www.who.int/mediacentre/factsheets/fs204/en/. Date accessed: 1/01/2017.
2. Chen CJ, Wang LY, Yu MW. Epidemiology of hepatitis B virus infection in the Asia-Pacific region. *J Gastroenterol Hepatol*. 2000;15(Suppl):E3-E6.
3. Yao JL. Perinatal transmission of hepatitis B virus infection and vaccination in China. *Gut*. 1996;38(Suppl 2):S37-S38.
4. Pan CQ, Zhang JX. Natural history and clinical consequences of hepatitis B virus infection. *Int J Med Sci*. 2005;2:36-40.
5. Xu Y, Liu H, Wang Y, Hao R, Li Z, Song H. The next step in controlling HBV in China. *BMJ*. 2013;347:f4503.
6. Boivin J, Bunting L, Collins JA, Nygren KG. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. *Hum Reprod*. 2007;22(6):1506-1512.
7. Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. *PLoS Med*. 2012;9(12):e1001356.
8. Rutstein SO, Shah IH. *Infecundity infertility and childlessness in developing countries*. World Health Organization; 2004.
9. Lao TT, Mak JSM, Li TC. Hepatitis B virus infection status and infertility causes in couples seeking fertility treatment-indicator of impaired immune response? *Am J Reprod Immunol*. 2017;77:e12636.
10. Jin L, Nie R, Li YF. Hepatitis B surface antigen in oocytes and embryos may not result in vertical transmission to offspring of hepatitis B virus carriers. *Fertil Steril*. 2016;105(4):1010-1013.
11. Mak JSM, Leung MBW, Chung CHS, et al. Presence of hepatitis B virus DNA in follicular fluid in female Hepatitis B carriers and

outcome of IVF/ICSI treatment: A prospective observational study. *Eur J Obstet Gynecol Reprod Biol*. 2019;239:11-15.
12. Hu XL, Zhou XP, Qian YL, Wu GY, Ye YH, Zhu YM. The presence and expression of the hepatitis B virus in human oocytes and embryos. *Hum Reprod*. 2011;26:1860e7.
13. Nie R, Jin L, Zhang H, Xu B, Chen W, Zhu G. Presence of hepatitis B virus in oocytes and embryos: a risk of hepatitis B virus transmission during *in vitro* fertilization. *Fertil Steril*. 2011;95:1667e71.
14. Kong Y, Liu Y, Liu XJ. Relationship between the mechanism of hepatitis B virus father-infant transmission and pregnancy outcome. *Arch Gynecol Obstet*. 2017;295(1):253-257.
15. Oger P, Yazbeck C, Gervais A, et al. Adverse effects of hepatitis B virus on sperm motility and fertilization ability during IVF. *Reprod Biomed Online*. 2011;23(2):207-212.
16. Zhou XP, Hu XL, Zhu YM, Qu F, Sun SJ, Qian YL. Comparison of semen quality and outcome of assisted reproductive techniques in Chinese men with and without hepatitis B. *Asian J Androl*. 2011;13(3):465-469.
17. Pirwany IR, Phillips S, Kelly S, Buckett W, Tan SL. Reproductive performance of couples discordant for hepatitis B and C following IVF treatment. *J Assist Reprod Genet*. 2004;21(5):157-161.
18. Wang LL, Li LF, Huang CY, et al. Maternal chronic hepatitis B virus infection does not affect pregnancy outcomes in infertile patients receiving first *in vitro* fertilization treatment. *Fertil Steril*. 2019;112(2):250-257.
19. Lee VCY, Ng EHY, Yeung WSBY, et al. Impact of positive hepatitis B surface antigen on the outcome of IVF treatment. *Reprod Biomed Online*. 2010;21(5):712-717.
20. Vicari E, Arcoria D, Di Mauro C, Noto R, Noto Z, La Vignera S. Sperm output in patients with primary infertility and hepatitis B or C virus; negative influence of HBV infection during concomitant varicocele. *Minerva Med*. 2006;97:65e77.
21. Guidelines for the prevention. *care and treatment of persons with chronic hepatitis B infection*. World Health Organization; 2015.
22. Chinese Society of Hepatology and Chinese Society of Infectious Diseases, Chinese Medical Association. The guideline of prevention and treatment for chronic hepatitis B (2010 version) [J]. *Chin J Hepatol*. 2011;19(1):13-24.
23. Chinese Society of Hepatology and Chinese Society of Infectious Diseases, Chinese Medical Association. The guideline of prevention and treatment for chronic hepatitis B: a 2015 update. *Zhonghua Gan Zang Bing Za Zhi*. 2015;23(12):888-905.
24. Chinese Society of Infectious Diseases and Chinese Society of Hepatology, Chinese Medical Association. The guidelines of prevention and treatment for chronic hepatitis B (2019 version). *Zhong hua Gan Zang Bing Za Zhi*. 2019;27(12):938-961.
25. Nelson NP, Jamieson DJ, Murphy TV. Prevention of perinatal hepatitis B virus transmission. *J Pediatric Infect Dis Soc*. 2014;3(Suppl 1):S7-S12.
26. Pan CQ, Duan Z, Dai E, et al. Tenofovir to prevent hepatitis B transmission in mothers with high viral load. *N Engl J Med*. 2016;374:2324e34.
27. Yu MM, Gu XJ, Xia Y, et al. Relationship between HBV cccDNA expression in the human ovary and vertical transmission of HBV. *Epidemiol Infect*. 2012;140:1454e60.
28. Han GR, Cao MK, Zhao W, et al. A prospective and open-label study for the efficacy and safety of telbivudine in pregnancy for the prevention of perinatal transmission of hepatitis B virus infection. *J Hepatol*. 2011;55:1215-1221.

How to cite this article: Yi W, Li M, Sun F, et al. Impact of in vitro fertilization-embryo transfer on mother-to-infant transmission in women with chronic HBV infection. *Liver Int*. 2022;42:2167-2174. doi: 10.1111/liv.15349