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The association of adverse outcomes in the mother with disease progression in offspring in families with clusters of hepatitis B virus infection and unfavorable prognoses in Northwest China

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Abstract

To investigate the transmission routes of hepatitis B virus (HBV) in families with clusters of infection and unfavorable prognoses and to analyze the prevalence of liver cirrhosis (LC) or hepatocellular carcinoma (HCC) in the offspring of these families.

Families with clusters of HBV infection and unfavorable prognoses were enrolled in the study, and general information and serum samples were collected. The prevalence of LC or HCC was compared in offspring of different genders whose parents were diagnosed with LC or HCC.

This analysis comprised 102 probands with 51 siblings, 15 parents, 284 children, and 74 spouses. Interestingly, 88.2% of the siblings and 76.8% of the children of these probands were positive for hepatitis B surface antigen (HBsAg), compared with only 9.5% of the spouses ($P < .001$). There were 266 nuclear families from 102 clustering families. The prevalence of LC or HCC in sons (44.8%) was higher than that in daughters (8.2%; $P < .05$) in families with mothers with LC or HCC, but there was no difference in families with fathers with LC or HCC. Moreover, the prevalence of LC or HCC in sons from families with mothers with LC or HCC (44.8%) was higher than in the families with fathers with LC or HCC (21.0%, $P = .016$).

The development of LC or HCC in offspring showed a greater relationship with the adverse outcomes induced by HBV infection in the mother compared with the father, and the prevalence of LC or HCC was much higher in male offspring.

Abbreviations: HBeAg = hepatitis B e antigen, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, LC = liver cirrhosis, MTIT = mother-to-infant transmission.

Keywords: adverse outcomes, family clustering, gender, hepatitis B virus, mother-to-child transmission

1. Introduction

Chronic hepatitis B virus (HBV) infection remains a major public health problem globally, particularly in Asia.[1] The 2017 World Health Organization Global Hepatitis Report estimates that 3.5% of the world population or 257 million people have chronic HBV infection.[2] In 2015, viral hepatitis led to 1.34 million deaths, 66% (884,400) was the result of HBV-related liver disease, including liver cirrhosis (LC), hepatocellular carcinoma (HCC), and acute hepatitis.[3]

According to previous studies, newborns have a 90% chance of becoming chronic carriers after infection with HBV.[4] It has been reported that more than 90% of infected infants follow a chronic course after HBV is acquired via mother-to-infant transmission (MTIT) in endemic areas.[5,6] MTIT plays an important role in intrafamilial transmission, which is synonymous with familial clusters of HBV infections. Moreover, MTIT of HBV was considered to exhibit a major intrafamilial transmission pattern and was associated with the development of HCC in offspring.[7,8] It was previously reported that approximately 70% of hepatitis B surface antigen (HBsAg)-positive patients with HCC acquired their HBV infection during the perinatal period.[9] But it is unknown about the outcomes of the disease in the different gender of the offspring.

Furthermore, father-to-child transmission also plays an important role in the prevalence of HBV. Epidemiological studies have shown that the incidence of father-to-child transmission ranges from approximately 9% to 13% in China.[10] And some studies have provided substantial evidence that HBV is transmitted from father to child at the molecular level based on homology and phylogenetic analyses.[8,11] HBV integration into sperm cells would create extensively inheritable

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effects because the fusion of these sperm with an ovum would result in HBV infection in newborn offspring and produce congenital or hereditary disease (e.g., embryonal tumor) by altering genetic constituents and/or inducing mutations.[12] Extensive studies have confirmed that the integration of HBV DNA into hepatocytes increases chromosome instability and causes genetic recombination and hepatocarcinogenesis.[13]

The study focus on such a special group, families with clusters of HBV infections and unfavorable prognoses which are defined as those families in which HBV-infected patients were present in 3 successive generations and more than 1 patient with HBV-associated LC or HCC was present in 2 generations. The characteristics of HBV infection and the development of disease in these special groups were assessed.[14] Few reports have examined the prevalence of HBV transmission from father–to-child among family members in China. The current study used the index patient and children in subsequent generations to assess the role of perinatal HBV transmission in severe complications of HBV infection. In this retrospective cohort study, differences in the prevalence of HBsAg and the incidence of LC or HCC in offspring between the children of female and male was evaluated, and the factors responsible for the unfavorable prognoses were determined in the clustering families.

2. Methods

2.1. Study cohort

The data collection and patient recruitment procedures have been reported in previous studies.[15] Briefly, the data were collected in Northwest China from 2007 to 2010. A total of 102 families with clusters of HBV infections and unfavorable prognoses were recruited. All subjects provided written informed consent and completed a structured case record form that was used for data collection by trained research assistants. The study was approved by the Research Ethics Committee (institutional review board) of the First Affiliated Hospital, Xi'an Jiaotong University, Shaanxi, China.

The diagnosis of chronic hepatitis B was determined in accordance with the following previously described criteria: patients were seropositive for HBsAg for at least 6 months, the serum HBV DNA concentration was >20,000 IU/mL for hepatitis B e antigen (HBeAg)-positive patients and >2000 IU/mL for HBeAg-negative patients, patients exhibited a persistent or intermittent increase in alanine aminotransferase levels, and patient liver biopsies displayed chronic hepatitis with moderate or severe necroinflammation. LC was diagnosed based on liver biopsy findings in HBsAg-positive subjects. If no baseline liver biopsy was available, then a classification was determined based on the clinical (presence of ascites or esophageal varices), biochemical (synthetic capacity of the liver), and imaging (regenerating nodules in the hepatic parenchyma, splenomegaly, and diameter of portal vein >14 mm) data available at study entry. HCC was diagnosed based on α-fetoprotein measurements and ultrasonography or computer tomography scans, and confirmed after a review of the patient's medical records.

2.2. Questionnaire

The demographic characteristics of the patients (gender; age; residence; education level; occupation; history of HBV vaccination; source of infection; marital status; HBsAg status of parents, spouses, and children; number and gender of children; and history of smoking or alcohol consumption), clinical signs, and treatment histories were collected. The questions contained a list of standardized, predefined answers that could be selected according to the accepted clinical and virological definitions. Data quality controls were performed by detecting potential duplications, logic errors, missing values, or unacceptable values.

2.3. Survey

Before any treatment, 5 mL blood was collected with a vacuum blood collection tube without anticoagulant. The serum was separated by centrifugation at 4°C and stored at −80C. The levels of serological markers of hepatitis B and antibodies against hepatitis C and hepatitis D virus were determined using an enzyme-linked immunosorbent assay kit (Wantai, Beijing, China). The hepatitis B viral loads were measured at the Institute of Hepatology of Xi'an Jiaotong University using the HBV fluorescence polymerase chain reaction diagnostic kit (Da An Gene Co., Ltd. of Sun Yat-Sen University, Guangzhou, China), which has a dynamic range of 10^2 to 10^8 IU/mL according to the manufacturer's instructions. Biochemical liver function was assayed using the Olympus AU5400 automatic biochemical analyzer (Olympus Corporation, Mishima, Japan). Serum alpha fetal protein levels (ng/mL) were measured using the automated Eleceyes platform (Roche Diagnostics, Mannheim, Germany), and liver ultrasonography or computer tomography scans were performed at each visit.

2.4. Statistical analysis

The data were analyzed using Epi-Info 2002 and SPSS 13.0 software. Comparisons among HBsAg-positive subjects (blood relatives of various degrees and spouses, sons and daughters with father and/or mother of HBsAg-positive, sons with LC and/or HCC, and daughters with LC and/or HCC with different outcomes of mother or father) were performed using the chi-square test or Fisher exact test. P-values $< .05$ were considered statistically significant.

3. Results

3.1. Clinical and virological characteristics of the study subjects

A total of 102 families with clusters of infection and unfavorable prognoses were recruited, including 102 probands, 402 first-degree relatives, 291 second-degree relatives, 48 third-degree relatives, 2 fourth-degree relatives, and 274 spouses. The prevalence of HBsAg in the blood relatives and spouses is shown in Table 1. The prevalence of HBsAg was 67.6% (571/845) in the blood relatives from families with clusters of infection and unfavorable prognoses was markedly higher than that in the spouses (8.4%, 23/274, $P < .001$) in the spouses. The prevalence of HBsAg gradually increased with age and was approximately 40.3%, 68.8%, 80.1%, and 72.9% in subjects less 20 years old, 20 to 40 years old, 40 to 60 years old, and more than 60 years old, respectively. The incidence of LC in the probands and first-degree blood relatives was higher than that in the spouses ($P < .05$), and the incidence of HCC in the probands was higher than that in the spouses ($P = .014$).

3.2. Prevalence of serological markers of HBV in family members

The prevalence of serological markers of HBV infection in the family members is shown in Figure 1. All probands and HBsAg-positive family members tested negative for anti-hepatitis C virus

Table 1

Comparison of HBsAg prevalence and clinical characteristics of blood relatives and spouses.

	No. (%)blood relatives	No. (%)spouses	*P*-values
Prevalence of HBsAg	571/845 (67.6%)	23/274 (8.4%)	<.001
Age			
<20	71/176 (40.3%)	0	
20–40	176/256 (68.8%)	8/81 (9.9%)	<.001
40–60	254/317 (80.1%)	11/128 (8.6%)	<.001
>60	70/96 (72.9%)	4/65 (6.2%)	<.001
LC	166/571 (29.1%)	2/23 (8.7%)	.059
Probands	58/102 (56.9%)		<.001
First-degree blood relatives	90/308 (29.2%)		.034
Second-degree blood relatives	17/143 (11.9%)		.925
HCC	98/571 (17.2%)	1/23 (4.3%)	.183
Probands	29/102 (28.4%)		.014
First-degree blood relatives	67/308 (21.8%)		.058
Second-degree blood relatives	2/143 (1.4%)		.363

HBsAg = hepatitis B surface antigen, HCC = hepatocellular carcinoma, LC = liver cirrhosis.

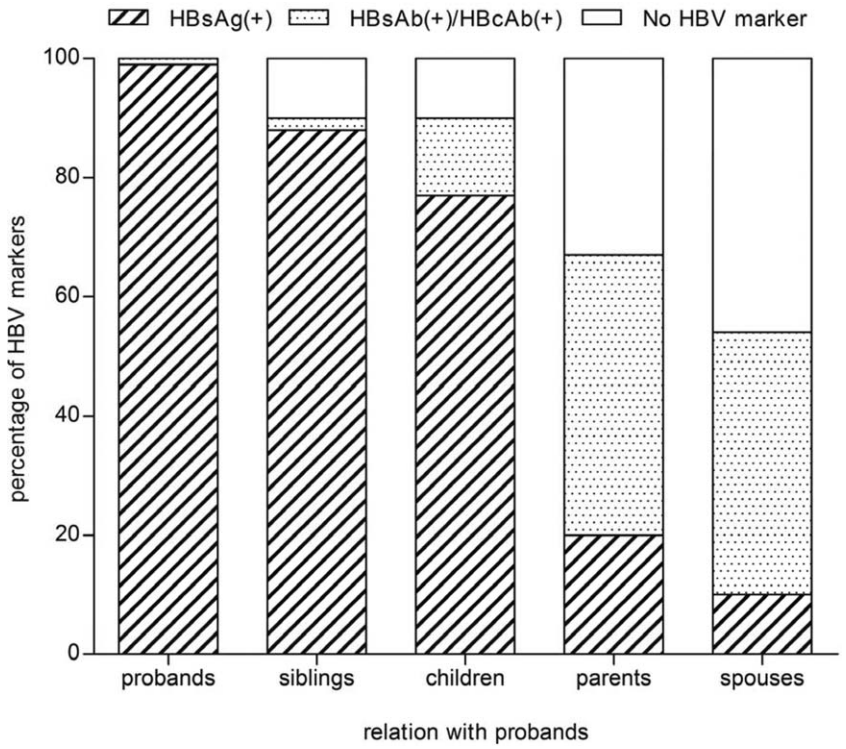

Figure 1. Hepatitis B serology among siblings, children, parents and spouses.

and anti-hepatitis D virus antibodies. The prevalence of serological markers of HBV infection among family members differed according to their relationship to the probands. The prevalence of HBsAg in siblings and children (88.2% and 76.8%, respectively) was significantly higher than that in the spouses (9.5%, $P < .001$). The prevalence of markers of HBV of past infection (HBsAb, hepatitis B surface antibody; HBcAb, hepatitis B core antibody; HBeAb, hepatitis B e antibody) and single anti-HBs were significantly increased in parents and spouses (46.6% and 44.6%, respectively, Fig. 1) in comparison to siblings and children (2.0% and 13.4%, respectively, $P < .001$).

3.3. Distribution of HBsAg in offspring from parents with different stages of HBsAg in nuclear families

There were 266 nuclear families from 102 clusters of infection with unfavorable prognoses, including 95 families with HBsAg-positive fathers, 148 families with HBsAg-positive mothers, and 23 families with HBsAg-positive fathers and mothers. There were 196 offspring in families with HBsAg-positive fathers, 388 offspring in families with HBsAg-positive mothers, and 53 offspring in families with HBsAg-positive fathers and mothers. The HBsAg-positive rate in the offspring was higher in families with HBsAg-positive mothers (77.1%) or both fathers and

Table 2

Prevalence of HBsAg in offspring from nuclear families.

	HBsAg (+) father HBsAg (−) mother	HBsAg (−) father HBsAg (+) mother	HBsAg (+) father HBsAg (+) mother	*P*-value
Number of nuclear family	95	148	23	
Number of offspring	196	388	53	
HBsAg (+) sons, %	37.4% (49/131)	77.5% (165/213)	80.8% (21/26)	<.05*
HBsAg (+) daughters, %	13.8% (9/65)	76.6% (134/175)	74.1% (20/27)	<.05*
HBsAg (+) offspring, %	29.6% (58/196)	77.1% (299/388)	77.4% (41/53)	<.05*

HBsAg = hepatitis B surface antigen.

* Compare with the HBsAg (+) father and the HBsAg (−) mother.

mothers (77.4%) than in families with HBsAg-positive fathers only (29.6%, $P < .001$) (Table 2). The prevalence of HBsAg in sons (37.4%) was higher than that in daughters (13.8%, $P = .001$) in families with HBsAg-positive fathers, but there were no differences in families with HBsAg-positive mothers (77.5% and 76.6%, respectively, $P = .835$) or both fathers and mothers (80.5% and 74.1%, respectively, $P = .560$).

3.4. Association with the progression of disease in offspring and unfavorable prognoses in fathers or mothers in nuclear families

There was a higher prevalence of the HBsAg in sons (42.9%, 46.0%, 44.7%, respectively) than in daughters (17.4%, 13.0%, 15.2%, respectively, $P < .05$) in families in which fathers had LC and/or HCC. However, the prevalence of HBsAg did not differ between the sons (88.1%, 87.5%, 87.9%, respectively) and daughters (87.3%, 83.3%, 85.9%, respectively, $P > .05$) in families in which the mothers had LC and/or HCC. There was an increased prevalence of LC in sons (13.6%) compared with daughters (0%, $P = .008$) in families with mothers with LC, whereas the prevalence of HCC was 23.7% and 0%, respectively ($P < .001$) (Fig. 2). Similarly, in families in which the mothers had HCC, the prevalence of LC in sons (32.1%) was higher than that in daughters (8.0%, $P = .043$), but there was no difference in the prevalence of HCC between sons and daughters (28.6% and 16.0%, respectively, $P = .377$). The prevalence of LC or HCC in sons (19.5% and 25.3%, respectively) was higher than that in daughters (2.7% and 5.5%, respectively, $P < .001$) in families with mothers with LC or HCC (Fig. 2). And the prevalence of LC or HCC in sons (17.4%) or in offspring (15.4%) from families with fathers with HCC was higher than in families with mothers with HCC (60.7%, $P = .002$; 43.4%, $P = .014$) (Table 3). Moreover, the prevalence of LC or HCC in sons from families with mothers with LC or HCC (44.8%) was higher than that in families with fathers with LC or HCC (21.1%, $P = .012$) (Table 3). However, there were no differences in prevalence of LC or HCC in sons or daughters between from families with fathers with LC and from families with mothers with LC (26.7% vs 37.3%, $P = .442$; 25% vs 0%, $P = .077$). And there were no differences in the prevalence of LC or HCC in daughters between from families with fathers with LC or HCC and mothers with LC or HCC (14.3% vs 8.2%, $P = .487$).

4. Discussion

The main routes of HBV transmission differ among endemic areas of HBV infection. HBV is highly prevalent (>8%) in East Asia, Pacific nations, and sub-Saharan Africa, the most common route of acquiring infection in these countries is perinatal transmission, or during preschool years; areas of intermediate prevalence (2%–7%) include parts of Central and Eastern Europe, the Middle East, Latin America as well as the Indian subcontinent, the main route of transmission is perinatal or horizontal; HBV is lower in prevalence (<2%) in North America and Western Europe, infection is usually spread through sexual contact or IV drug use.[16] In China, which is a moderately endemic country, MTIT remains a leading cause of HBV infection, accounting for 40% of total infections, although the prevalence of HBsAg was reported to be 9.75% in 1992 and 7.18% in 2006.[17] Therefore, family screening is important in countries with moderately and highly endemic regions.

Until now, routes of HBV transmission within families have been unclear. Some research has demonstrated that horizontal routes are the main routes of transmission among families, including kissing on the lips or sharing chewing gum and candy. The prevalence of HBsAg positivity in mothers, fathers, and siblings of patients with chronic hepatitis B has been reported to be 14.7% to 38%, 17.7% to 23%, and 10.9% to 25.2%, respectively.[18,19] In the current study, the prevalence of HBsAg positivity in the parents, siblings, and children of the probands was 20%, 88.2%, and 76.8%, respectively. Thus, both vertical and horizontal transmission was the main routes of transmission in families with clusters of infections and unfavorable prognoses. The prevalence of HBsAg in children was 76.8%, which was higher than that in spouses and possibly related to the observation that vertical transmission is the main transmission route in cluster families. Moreover, the majority of the probands and their family members had a low socio-economic status and were from distant countryside areas of Northwestern China, where the rate of vaccination is still lower than that in cities. The prevalence of HBsAg in siblings was high and similar to the children. There are several possible reasons for this observation. First, vertical transmission remains the most important mode of HBV transmission among siblings. However, the prevalence of HBsAg in their parents was low, which was associated with the older age of the probands and absence of data for the prevalence of HBsAg in their parents because most of their parents were deceased. Second, most family members from rural areas shared personal items, such as clothes, bath towels, and eating and drinking utensils, demonstrating that horizontal transmission may be an important factor related to the intrafamily clusters of HBV infections in this study group.

In the present study, we observed that the rates of HBsAg positivity in the offspring were 29.6% (only the father was HBsAg-positive), 77.1% (only the mother was HBsAg-positive), and 77.4% (both the mother and father were HBsAg-positive). Therefore, MTIT is still a major transmission pattern in cluster families. The risk of chronic infection is inversely proportional to

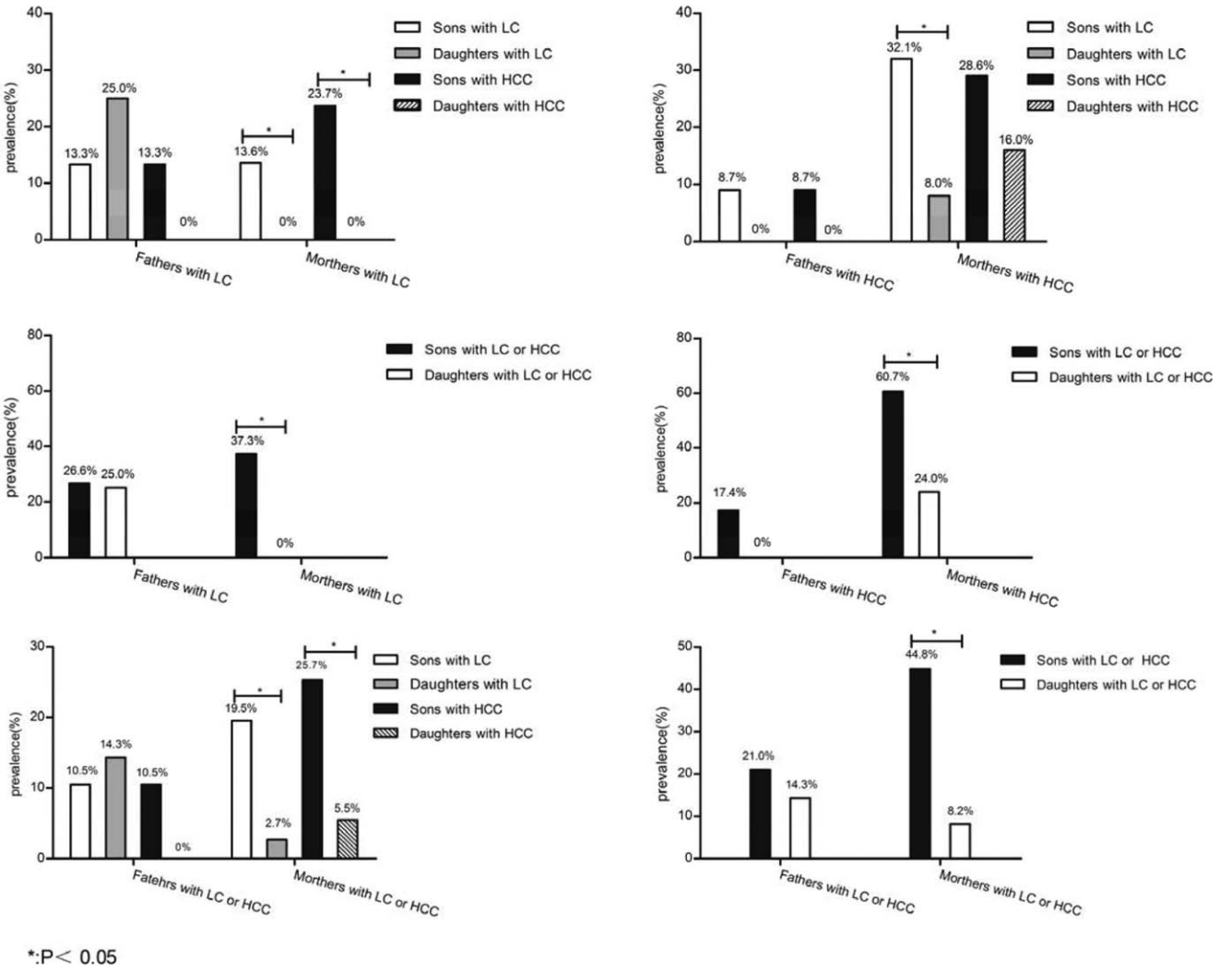

Figure 2. Distribution of LC or HCC in offspring from nuclear families with adverse outcomes in fathers or mothers. HCC = hepatocellular carcinoma, LC = liver cirrhosis.

the age at which the infection is acquired. As many as 90% of infants who acquire HBV infection from their mothers fail to clear the infection and, consequently, develop chronic infection,[4] which may be one of the reasons for the adverse outcomes in the study group. Since the development of HBV vaccines and hepatitis B immunoglobulin (HBIG) in the 1980s, approximately 90% of mother-to-infant HBV transmission can be blocked.[6] In addition, the high level of maternal HBV DNA with HBeAg positivity correlated with immunoprophylaxis failure despite of adequate combination HBIG and HBV vaccination, the use of antiviral therapy in the second or third trimester has been shown to be safe and tolerable for reducing the incidence of MTIT in pregnant women with high HBV DNA loads.[20] However, the prevalence of HBsAg remains high in cluster families with

Table 3

Progression of disease in offspring from nuclear families in fathers or mothers with adverse outcome.

	Offspring		HBsAg (+)		LC or HCC					
	Sons	Daughters	Sons	Daughters	Sons	*P*-values	Daughters	*P*-values	Offspring	*P*-values
Fathers with LC	35	23	15 (42.9%)	4 (17.4%)	4 (26.7%)		1 (25%)		5 (26.3%)	
Mothers with LC	67	55	59 (88.1%)	48 (87.3%)	22 (37.3%)	.442	0	.077	22 (20.6%)	.795
Fathers with HCC	50	23	23 (46.0%)	3 (13%)	4 (17.4%)		0		4 (15.4%)	
Mothers with HCC	32	30	28 (87.5%)	25 (83.3%)	17 (60.7%)	**.002**	6 (24.0%)	1.000	23 (43.4%)	**.014**
Fathers with LC or HCC	85	46	38 (44.7%)	7 (15.2%)	8 (21.1%)		1 (14.3%)		9 (20.0%)	
Mothers with LC or HCC	99	85	87 (87.9%)	73 (85.9%)	39 (44.8%)	**.012**	6 (8.2%)	1.000	45 (28.1%)	.274

HBsAg = hepatitis B surface antigen, HCC = hepatocellular carcinoma, LC = liver cirrhosis.

unfavorable prognoses due to the absence of detection throughout pregnancy, low coverage of timely birth dose, intrauterine infection, and immunoprophylaxis failure. MTIT is associated with more severe morbidity and mortality than horizontal transmission. Chronic infections and subsequent complications, that is, cirrhosis and HCC, are more likely to occur in persons infected during infancy or early childhood. Therefore, with the current dramatic decrease in prevalence of HBsAg in the general population, attention should be focused on special populations, which represent the key point for the future eradication of MTIT of HBV.

Perinatal transmission of the virus from HBV carrier mothers to their children is generally considered the major mode of transmission in China. However, the rate of HBsAg positivity was 29.6% in children from families with HBsAg-positive fathers, suggesting that father-to-child transmission is also a significant route of HBV infection in cluster families with unfavorable prognoses. The rate of father-to-child transmission in this study was higher than that in previous studies, in which the values ranged from 9% to 13%.[21] Some research has suggested that HBV DNA can integrate into sperm chromosomes, indicating that infants with an HBsAg-positive father are a high risk group for vertical transmission from their father.[21–23] Other studies have indicated that the main route of father-to-child transmission may be horizontal. Skin lesions or contaminated material, such as towels, toothbrushes, or razor blades, may play a role in this route of transmission.[24] Because the present study was retrospective and there were no data concerning the HBsAg status of the neonates, we could not determine with certainty the route of father-to-child transmission. To institute reasonable management practices and decrease HBV transmission from father to child, prospective studies must be designed in the future to evaluate the main father-to-child transmission routes in families with clusters of infections and unfavorable prognoses.

Chronic HBV infection is a serious clinical problem because of its adverse sequelae, including LC and HCC. In addition to host factors, viral factors have been shown to influence the clinical outcomes of chronic HBV infection because HBV infection via perinatal transmission is also important in hepatocarcinogenesis.[25] In the current study, we obtained the same results, demonstrating that the development of LC or HCC in offspring had a greater relationship with HBV infection in the mother than in the father.[7,8] There are several explanations for why perinatal transmission determined the outcome of chronic HBV infection. First, perinatal transmission induces a high tolerance to HBV. Second, a high dose of HBV DNA via perinatal transmission can increase tolerance to HBV during early stages of life. Finally, persistent HBV infection generally causes repeated hepatic necrotic-inflammatory activities and regeneration, which is one of the main causes of hepatocarcinogenesis.[26] Therefore, a number of initiatives are needed to improve the prevention of perinatal HBV infection in cluster families. However, it is more important to note the gender difference in the prevalence of HBsAg and the incidence of LC or HCC in offspring. The results demonstrated a higher incidence of LC or HCC in male offspring (44.8%) than in female offspring (8.2%) of mothers with HBV-associated LC or HCC. The gender difference in the prevalence of HBsAg in children of HCC patients has been reported, but there are few reports concerning the gender differences in HBsAg prevalence in offspring that are accompanied by adverse sequelae in families in which the mother has LC or HCC. Therefore, males from families in which the mother has LC or HCC may be at a higher risk for disease progression than females, and it is possible that the difference in gender prevalence is associated with sex hormones. Other factors, such as higher immunity in females than males, may also contribute to HBsAg clearance.

In conclusion, in families with clusters of infections and unfavorable prognoses, both vertical transmission and horizontal transmission were found to be main routes of transmission. Although father-to-child transmission played a role in HBV transmission in families, MTIT was still the main route of transmission. The development of LC or HCC in offspring showed a greater relationship with HBV-induced adverse outcomes in the mother than in the father, and the prevalence of adverse outcomes in male offspring was higher than that in female in families in which the mother has LC or HCC.

Author contributions

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