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ORIGINAL ARTICLE

Prevalence and clinical features of hepatitis E virus infection in pregnant women: A large cohort study in Inner Mongolia, China

Xiao-xia Ma[a,1], Yunpeng Ji[a,b,c,1], Li Jin[a], Zulqarnain Baloch[a], De-rong Zhang[a], Yijin Wang[d], Qiuwei Pan[a,c,], Zhongren Ma[a,*]**

[a] *Key Laboratory of Biotechnology and Bioengineering of State Ethnic Affairs Commission, Biomedical Research Center, Northwest Minzu University, Lanzhou, China*
[b] *Department of Genetics, Inner Mongolia Maternal and Child Care Hospital, Hohhot, Inner Mongolian Autonomous Region, China*
[c] *Department of Gastroenterology and Hepatology, Erasmus MC-University Medical Center, Rotterdam, The Netherlands*
[d] *Department of Pathology and Hepatology, The 5th Medical Center, Chinese PLA General Hospital, Beijing, China*

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Abstract
Background and aim. — Hepatitis E virus (HEV) infection causes severe maternal and fetal outcomes in pregnant women. These patients are exclusively from resource-limited regions with genotype 1 HEV infection, but not from western countries with genotype 3 prevalence. Since the circulating strains in China have evolved from the waterborne genotype 1 to the zoonotic genotype 4 HEV in the past decades, this study aims to evaluate the prevalence and clinical features of HEV infection in a large cohort of pregnant women in Inner Mongolia, China.
Methods. — A total of 3278 pregnant women who visited the Inner Mongolia Maternal and Child Care hospital during 2018 were enrolled. Serum samples were examined for anti-HEV IgG and anti-HEV IgM antibodies using ELISA. Demographic information, results of clinical biochemical tests, maternal and neonatal outcomes were collected.

Abbreviations: HEV, hepatitis E virus ;FHF, fulminant hepatic failure ;AST, aspartate aminotransferase ;ALT, alanine aminotransferase.

* Corresponding author at: Northwest Minzu University, Room Na-100, Lanzhou, 730030, China.
** Corresponding author at: Erasmus MC, Room Na-1005, Wytemaweg 80, NL-3015 CN, Rotterdam, The Netherlands.
Adresses e-mail : q.pan@erasmusmc.nl (Q. Pan), mzr@xbmu.edu.cn (Z. Ma).

[1] These authors contributed equally.

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Results. — Among the recruited 3278 pregnant women, 6.0% were anti-HEV IgG antibody positive, 0.3% were anti-HEV IgM antibody positive and 0.3% were positive for both anti-HEV IgG and anti-HEV IgM antibodies. HEV viral RNA was not detected. Pregnant women with recent/ongoing HEV infection indicated by anti-HEV IgM positivity have slightly higher ALT level, and potential risk of developing hyperlipidemia, preterm delivery and neonatal jaundice.
Conclusions. — These findings indicated that HEV infection is associated with a possible increase in adverse maternal, fetal and neonatal outcomes in our cohort. Thus, the burden of HEV infection in pregnant women in China appears distinct from resource-limited regions and western countries. Nevertheless, future studies are required to confirm and extend our findings.

Introduction

Hepatitis E virus (HEV) is a positive-sense, single-stranded RNA virus that represents as a leading cause of acute viral hepatitis globally. There is only one single serotype of HEV, but classified into eight genotypes. Anti-HEV IgM antibodies can be detected shortly after the infection followed by the appearance of anti-HEV IgG antibodies. The presence of anti-HEV IgM antibodies indicates recent/ongoing infection, whereas the presence of IgG antibodies alone indicates previous infection [1]. Genotypes 1 and 2 HEV exclusively infecting humans are found mainly in developing countries, and responsible for many water-borne outbreaks. In contrast, HEV genotypes 3 and 4 are zoonotic and responsible for sporadic infections mainly in developed countries [2—5].

Although HEV infection is usually acute and self-limiting in the general population, infection in pregnant women can cause severe outcomes including fulminant hepatic failure (FHF) with fatality rate up to 30% [6]. FHF resulted from fulminant hepatitis is the main cause of high death rate among pregnant women, especially in the third trimester [7—9]. These patients are almost exclusively from recourse-limited regions with genotype 1 HEV infection, but not from western countries with prevalence of genotype 3 HEV. Recently, studies from Namibia and China have indicated that genotype 2 and 4 HEV can also negatively affect the clinical outcomes of pregnant women [4,10].

China is an endemic area for HEV. In 1991, there was a large outbreak occurred in Xinjiang provide, caused by genotype 1 HEV. The attack rate in pregnant women was significantly higher than that of the non-pregnant population. This resulted in severe clinical outcomes in pregnant patients, with fatality rate of 5.88% and abortion rate of 17.64% [6,11]. Of note, the epidemiology of HEV is dramatically changing in China. Currently, genotype 4 instead of 1 is circulating in the population. It is zoonotic and supposed to be more pathogenic [12]. This study aims to investigate the prevalence and clinical features of HEV in a large hospital-based population cohort of pregnant women in Inner Mongolian. Inner Mongolian is one of the five autonomous regions for ethnic minorities in China, including Han, Mongolian, Hui, Ewenki Manchu and Daur. It is a less-developed area with animal husbandry as the mainstay of economy. Therefore, this region is ideal for studying diseases associated with genetics, environmental factors and life styles.

Materials and methods

Study design

Pregnant women who visited the Inner Mongolia Maternal and Child Care hospital from January to December, 2018 were enrolled. Demographic information, results of clinical biochemical tests, maternal and neonatal outcomes were collected from the hospital's computerized pregnancy information database. A control non-pregnant cohort of 290 participants who attended physical examination in Inner Mongolia was included. The records of all participants were anonymously analyzed. All participates provided informed consent that allow future testing of archived bio-samples including leftover serum. This study was approved by ethical committee of Inner Mongolia Maternal and Child Care Hospital, and Northwest Minzu University, China.

Laboratory tests of HEV infection

Serum samples of pregnant women were screened for the presence of anti-HEV IgG and IgM antibodies using commercially-available enzyme immunoassay kits (Wantai Biological Pharmacy Enterprise, Beijing, China). Every 30 samples were pooled for detecting HEV viral RNA by conventional qRT-PCR. All anti-HEV IgM positive samples were again tested for HEV RNA using commercially available Fluorescence Quantitative PCR kit (Beijing Kinghawk Pharmaceutical CO., LTD, Beijing, China) according to the manufacturer's instructions.

The anti-HEV IgM antibody positive and HEV RNA negative samples were further tested using nested RT-PCR. Total RNA was extracted from the serum using the QIAamp Viral RNA mini-kit (Qiagen, Germany) according to the manufacturer's instructions. cDNA was synthesized from 8 μl purified RNA using 2 μl reverse transcriptase (promega, USA). A nest-PCR was carried out to produce a 348-nucleotide amplicon from HEV open reading frame 2 (ORF2). Briefly, the first round PCR was in a 20 μl reaction, including 5 μl cDNA, 10 μl Green Taq Mix (Takara, Japan), 1 μl primers (Forward, 5′-AATTATGCYCAGTAYCGRGTTG-3′. Reverse, 5′—CCCTTA(G)TCC(T)TGCTGA(C)GCATTCTC-3′) and 4 μl ddH_2O. The PCR parameters including a denaturation step at 94 °C for 5 min, followed by 35 cycles of denaturation for 30 s at 94 °C, annealing for 30 s at 42 °C, extension for 50 s at 72 °C, and a final incubation at 72 °C for 5 min. The second-round PCR was performed using

5 μl of first-round PCR product and internal primers (forward, 5′-GTT(A)ATGCTT(C)TGCATA(T)CATGGCT-3′. reverse, 5′-AGCCGACGAAATCAATTCTGTC -3′), and parameters were the same with that in the first-round, except shortening the extension time to 30 s.

Statistical analysis

SPSS version 13.0 (Chicago, IL, USA) was used to perform all the statistical analysis. Statistical analysis was performed by univariate analysis. Significance was set at $P<0.05$.

Results

HEV sero-prevalence

In total, 3278 pregnant women were enrolled for HEV screening. The overall sero-prevalence of anti-HEV IgG and IgM antibodies was 6.62% (217/3278). 6.0% (196) were anti-HEV IgG antibody positive IgM antibody negative, indicating past HEV infection. 0.62% (21) were anti-HEV IgM antibody positive, including 10 anti-HEV IgM and IgG positive and 11 anti-HEV IgM positive IgG negative, indicating recent/ongoing infection (Fig. 1). In the non-pregnant cohort, 13 out of 290 samples (4.5%) were positive for anti-HEV IgG, but none was positive for anti-IgM antibody (Supplementary Table 1). Detection of HEV RNA in patient blood and stool is essential to conform the active infection [1]. However, we were not able to detect viral RNA by pool of every 30 serum samples and in any of the individual anti-HEV IgM antibody positive serum samples, whereas stool samples were not available for these participants.

Demographic characteristics and potential association with recent/ongoing HEV infection

We next performed analysis on the characteristics of HEV sero-positive pregnant women (Table 1). We focused on the nested-cohort of the 217 sero-positive participates, and this enabled us to compare the differences between recent/ongoing with past infection as the control. All 217patients were classified into four groups according to the status of anti-HEV IgG or/and IgM antibody positivity. There is no significant difference regarding pregnant trimester, mean age, childbearing history, residence area and profession. Interestingly, ethnicity in particular Tujia people appears to have higher rate of recent/ongoing infection (IgM antibody positivity). But this sub-population is too small to draw firm conclusion.

Blood biochemical profiling

Regarding blood biochemical parameters, there is no significant difference for mean hemoglobin, mean platelet count, mean serum albumin level, median aspartate aminotransferase (AST) level and median alkaline phosphatase level. Interestingly, median alanine aminotransferase (ALT) level among anti-HEV IgM positive group is significantly higher compared with that in the IgG antibody positive IgM antibody negative population (Table 2). Because the level of ALT increase is very mild, it is difficult to conclude whether this is related to possible induction of liver injury by HEV infection.

Pregnancy complications

To assess the potential impact of HEV infection on maternal outcome, we analyzed eight variables including postpartum hemorrhage, premature rupture of membranes, maternal mild anemia, intrauterine asphyxia, pregnant hypertension, pregnant hyperlipidemia, gestational diabetes mellitus and severe preeclampsia. No significant differences were observed between anti-HEV IgM antibody positive and the control group, except for pregnant hyperlipidemia at the second trimester ($P = 0.03$) (Table 3). None of the sero-positive pregnant women died in our study.

Fetal and neonatal outcomes

To finally assess the impact on fetal and neonatal outcomes, eight variables were analyzed, including preterm delivery, mean Apgar values, precipitate labour, caesarean section, neonatal weight, neonatal death, neonatal retinal hemorrhage and neonatal jaundice. The rates of preterm delivery and neonatal jaundice appear to be higher in anti-HEV IgM antibody positive compared to the anti-HEV IgG antibody positive IgM antibody negative control group (Table 4).

Discussion

The overall sero-prevalence of HEV was 6.62% in our large cohort of over 3,000 pregnant women in Inner Mongolia China. 6.0% of the samples were anti-HEV IgG antibody positive, 0.3% were anti-HEV IgM antibody positive, and 0.3% were positive for both anti-HEV IgG and anti-HEV IgM antibodies. In our non-pregnant control cohort, we found a prevalence rate of anti-HEV IgG antibody as 4.5%. This is comparable but slightly lower than that in pregnant women. Of note, the average age (18.84 ± 0.78 years old) of the control group is slightly younger than the average pregnant age (about 26) in China (Supplementary Table 1). It is well-recognized that age is associated with anti-HEV IgG prevalence [1], but we were not able to find a perfectly age-matched control cohort.

The sero-prevalence in our pregnant cohort is relatively lower than the average level (11.66—41.71% for IgG and 0.43—2.8 % for IgM) in the general population in China [13], suggesting that pregnancy itself is likely not a risk factor of HEV infection. It is also lower than the average level of Chinese pregnant women reported in other studies, which is 10.24—16.2% for IgG and 2.56—3.2% for IgM [14,15]. Our overall sero-prevalence rate is much lower than the results of similar studies done in Egypt (84.3%), Sudan (41%), India (33.6%) and other developing countries [16—18]. In these endemic regions, HEV is predominantly transmitted via the faecal-oral route due to water contamination. This is especially common in rural areas having poor sanitation [19]. In China, local sanitation standards have been greatly improved during the past decades. With changes of the circulating genotype, HEV is mainly transmitted through contamina-

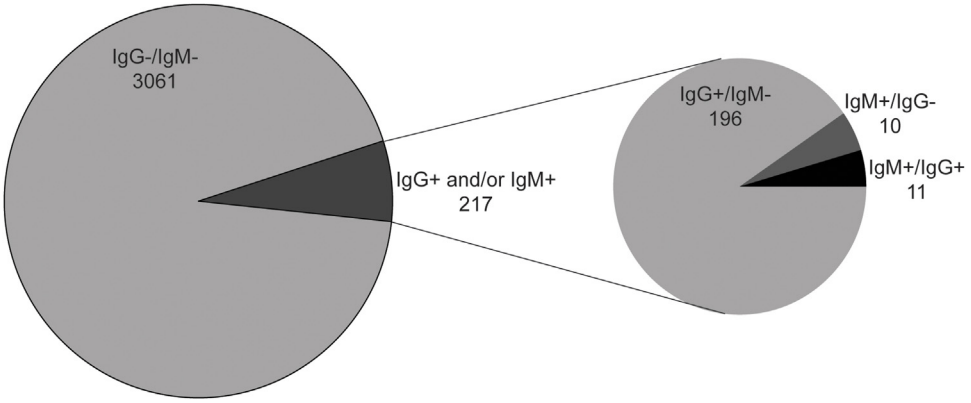

Figure 1 Study population and HEV sero-prevalence.
3278 pregnant women were recruited and screened for HEV sero-prevalence. Among these participants, 6.0% were anti-HEV IgG antibody positive, 0.3% were anti-HEV IgM positive, and 0.3% were positive for both anti-HEV IgG and anti-HEV IgM, respectively.

Table 1 Demographic characteristics according to anti-HEV IgG or/and IgM antibody positivity and factors potentially associated with recent/ongoing HEV infection.

Variables	IgM^+IgG^-	IgM^+IgG^+	(IgM^+IgG^-) & (IgM^+IgG^+)	IgG^+IgM^-	P value		
	(n = 11)	(n = 10)	(n = 21)	(n = 196)	(IgM^+IgG^-) vs (IgG^+IgM^-)	(IgM^+IgG^+) vs (IgG^+IgM^-)	$(IgM^+IgG^-$ & $IgM^+IgG^+)$ vs (IgG^+IgM^-)
Trimester, n(%)							
First trimester	8 (72.7)	9 (90)	17 (81)	103 (52.6)	0.497	0.338	0.212
Second trimester	3 (27.3)	1 (10)	4 (19)	93 (47.4)	0.398	0.081	0.093
Mean age(SD), y	28 (2.4)	27 (3.8)	28 (3.2)	28 (3.4)	0.875	0.294	0.423
Childbearing history (SD)							
Mean gravida	0.9 (0.3)	0.67 (0.7)	0.82 (0.5)	0.74 (0.8)	0.542	0.835	0.719
Mean para	0.2 (0.4)	0.17 (0.3)	0.18 (0.4)	0.19 (0.4)	0.965	0.879	0.935
Ethnics, n(%)							
Han	7 (63.6)	7 (70)	14 (66.7)	160 (81.6)	0.614	0.76	0.574
Mongolian	3 (27.2)	1 (10)	4 (19)	26 (13.3)	0.283	0.791	0.534
Hui	1 (9.1)	0 (0)	1 (4.8)	5 (2.6)	0.234		0.571
Man	0 (0)	1 (10)	1 (4.8)	4 (2)		0.132	0.445
Tujia	0 (0)	1 (10)	1 (4.8)	1 (0.5)		**0.005**	0.059
Residence area, n(%)							
Urban	11 (100)	9 (90)	20 (95.2)	175 (89.3)	0.796	0.987	0.845
Rural	0 (0)	1 (10)	1 (4.8)	21 (10.7)		0.949	0.428
Profession, n(%)							
Job	6 (54.5)	7 (70)	13 (61.9)	156 (79.6)	0.464	0.799	0.495
No job	5 (45.6)	3 (30)	8 (38.1)	40 (20.4)	0.148	0.569	0.16

ted food and causes sporadic infection by genotype 4 HEV [20,21].We failed to detect HEV RNA, and therefore were not able to confirm the genotype. However, genotype 4 HEV has been widely detected in neighboring regions of Inner Mongolia [22—24].

The low prevalence of HEV in Inner Mongolia may be associated with their dietary habit and life style. This region has large sheep and cow, but not swine farming. The local people mainly feed on mutton and milk products, whereas pigs are the main reservoir for food-borne transmission of HEV, although the host for HEV is not only restricted to swine [2]. We evaluated several factors including trimester, mean age, childbearing history, residence area and profession, but these were not associated with HEV infection. There may be potential relation with ethnicity that Tujia group appears to have higher rate of recent/ongoing infection. However, Tujia is not the main ethnicity in Inner Mongolia China and there is very limited patient number in our study to draw firm conclusion.

Severe clinical outcomes in pregnant women infected with HEV have been exclusively recorded from Asian and African countries, in particular resource-limited regions. In

Table 2 Blood biochemical profiles according to anti-HEV IgG or/and IgM antibody positivity.

Variables	IgM^+IgG^-	IgM^+IgG^+	(IgM^+IgG^-) & (IgM^+IgG^+)	IgG^+IgM^-	P value		
	(n = 11)	(n = 10)	(n = 21)	(n = 196)	(IgM^+IgG^-) vs (IgG^+IgM^-)	(IgM^+IgG^+) vs (IgG^+IgM^-)	(IgM^+IgG^-& IgM^+IgG^+) vs (IgG^+IgM^-)
Mean hemoglobin level (SD), g/l	129 (8.5)	125 (6.3)	127 (7.9)	127 (10.8)	0.668	0.565	0.985
Median leukocyte count (range), cells $\times 10^9$/l	8.9 (5.6–15.3)	8.1 (5.5–12.7)	10.9 (5.5–15.3)	9.8 (4.4–15.6)	0.364	0.253	0.135
Mean platelet count (SD), cells $\times 10^9$/l	220.9 (55)	238.1 (49)	227.6 (53)	259.9 (48)	0.097	0.651	0.126
Mean serum bilirubin level (SD)	6.6 (3.0)	8.73 (4.1)	7.6 (3.7)	6.93 (3.8)	0.809	0.226	0.521
Mean serum albumin level (SD), g/l	41.6 (2.1)	41 (4.7)	41.3 (3.6)	42.14 (2.7)	0.561	0.304	0.276
Median alanine aminotransferase level (range), U/l	18.5 (12.2–22.9)	19.9 (12.6–23.5)	18.7 (12.2–23.5)	14.1 (4.2–47)	**0.028**	**0.049**	**0.02**
Median aspartate aminotransferase level (range), U/l	16.2 (10.5–25)	17.5 (12.2–30.2)	17.5 (10.5–30.2)	16.1 (9.2–51.9)	0.479	0.649	0.712
Median alkaline phosphatase level (range), U/l	47 (28.3–67.5)	49.1 (39.6–164.6)	49.1 (28.3–164.6)	51.6 (19.3–100.4)	0.479	0.699	0.417

Table 3 Comparison of the risk of obstetric complications.

Variables	IgM^+IgG^-	IgM^+IgG^+	(IgM^+IgG^-) & (IgM^+IgG^+)	IgG^+IgM^-	P value		
	(n = 11)	(n = 10)	(n = 21)	(n = 196)	(IgM^+IgG^-) vs $(IgG^+ IgM^{-})$	(IgM^+IgG^+) vs $(IgG^+ IgM^-)$	$(IgM^+IgG^-$ & $IgM^+IgG^+)$ vs (IgG^+IgM^-)
Postpartum hemorrhage, n/n (%)	0 (0)	0 (0)	0 (0)	2/196 (1)			
First trimester	0 (0)	0 (0)	0 (0)	2/103 (1.9)			
Second trimester	0 (0)	0 (0)	0 (0)	0/93 (0)			
Premature rupture of membranes, n/n (%)	1/11 (9.1)	4/10 (40)	5/21 (23.8)	43/196 (22)	0.391	0.323	0.876
First trimester	1/8 (12.5)	3/9 (33.3)	4/17 (23.5)	24/103 (23.3)	0.56	0.61	0.987
Second trimester	0/3 (0)	1/1 (100)	1/4 (25)	19/93 (20.4)		0.115	0.86
Maternal mild anemia (Hb 90−110 g/dl), n/n (%)	5/11 (45.5)	1/10 (10)	6/21 (28.6)	51/196 (26)	0.315	0.35	0.848
First trimester	5/8 (62.5)	1/9 (11.1)	6/17 (35.3)	35/103 (34)	0.306	0.274	0.941
Second trimester	0 (0)	0 (0)	0 (0)	16/93 (17.2)			
Intrauterine asphyxia, n/n (%)	1/11 (9.1)	0 (0)	1/21 (4.8)	11/196 (5.6)	0.655		0.878
First trimester	1/8 (12.5)	0 (0)	1/17 (5.9)	6/103 (5.8)	0.494		0.993
Second trimester	0 (0)	0 (0)	0 (0)	5/93 (5.4)			
Pregnant hypertension, n/n (%)	0 (0)	0 (0)	0 (0)	4/196 (2.0)			
First trimester	0 (0)	0 (0)	0 (0)	3/103 (2.9)			
Second trimester	0 (0)	0 (0)	0 (0)	1/93 (1.1)			
Pregnant hyperlipidemia, n/n (%)	0 (0)	1/10 (10)	1/21 (4.8)	3/196 (1.5)		0.073	0.31
First trimester	0 (0)	0 (0)	0 (0)	2/103 (1.9)			
Second trimester	0 (0)	1/1 (100)	1/4 (25)	1/93 (1.1)		**<0.001**	**0.03**
Gestational diabetes mellitus, n/n (%)	0 (0)	0 (0)	0 (0)	12/196 (6.1)			
First trimester	0 (0)	0 (0)	0 (0)	5/103 (4.9)			
Second trimester	0 (0)	0 (0)	0 (0)	7/93 (7.5)			
Severe preeclampsia, n/n (%)	0 (0)	0 (0)	0 (0)	2/196 (1.0)			
First trimester	0 (0)	0 (0)	0 (0)	2/103 (1.9)			
Second trimester	0 (0)	0 (0)	0 (0)	0 (0)			

Table 4 Comparison of fetal/neonatal outcomes.

Variables	IgM^+IgG^-	IgM^+IgG^+	(IgM^+IgG^-) & (IgM^+IgG^+)	IgG^+IgM^-	P value		
	(n = 11)	(n = 10)	(n = 21)	(n = 196)	(IgM^+IgG^-) vs (IgG^+IgM^-)	(IgM^+IgG^+) vs (IgG^+IgM^-)	$(IgM^+IgG^-$ & $IgM^+IgG^+)$ vs $(IgG^+$ $IgM^-)$
Preterm delivery(<37 w)	1/11 (9.1)	2/10 (20)	3/21 (14.3)	7/196 (3.6)	0.385	0.026	0.041
Mean Apgar values (SD)	9.4 (0.5)	9.2 (0.4)	9.3 (0.4)	9.1 (0.4)	0.331	0.758	0.287
Precipitate labour, n (%)	0 (0)	0 (0)	0 (0)	3/196 (1.5)	–	–	–
Neonatal deaths, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	–	–	–
Caesarean section, n/n (%)	1/11 (9.1)	2/10 (20)	3/21 (14.3)	47/196 (24)	0.341	0.818	0.412
First trimester	1/8 (12.5)	1/9 (11.1)	2/17 (11.8)	28/103 (27.2)	0.462	0.332	0.269
Second trimester	0 (0)	1/1 (100)	1/4 (25)	19/93 (20.4)		0.223	0.86
Neonatal weight (SD), g	3490 (504)	3333 (302)	3404 (414)	3356 (422)	0.496	0.896	0.719
Neonatal retinal hemorrhage, n/n (%)	1/11 (9.1)	1/10 (10)	2/21 (9.5)	6/196 (3.1)	0.31	0.267	0.361
First trimester	1/8 (12.5)	1/9 (11.1)	2/17 (11.8)	5/ 103 (4.9)	0.397	0.46	0.299
Second trimester	0 (0)	0 (0)	0 (0)	1/93 (1.1)	–	–	–
Neonatal jaundice, n/n (%)	3/11 (18.2)	1/10 (10)	4/21 (19)	9/196 (4.6)	0.07	0.47	**0.018**
First trimester	3/8 (25)	1/9 (11.1)	4/17 (23.5)	7/103 (6.8)	0.016	0.659	0.055
Second trimester	0 (0)	0 (0)	0 (0)	2/93 (2.2)	–	–	–

outbreak settings, HEV infection results in worse maternal and fetal outcomes, including jaundice, malaise, anorexia, hepatalgia, nausea, vomiting and lethargy [6,25—27]. In hospital-based settings, pregnant women showing jaundice due to acute viral hepatitis have higher rates of FHF and mortality compared to women without HEV infection [10,28]. HEV infected pregnant women also have a significantly higher risk of developing obstetric complications, and poor fetal and neonatal outcomes [29—31].

The largest HEV outbreak lasting from September 1986 to April 1988 was reported from Xinjiang, China. 120,000 suspected and 707 death cases were recorded with an overall attack rate of 3.0%. The attack rate in pregnant women was significantly higher resulting in severe clinical outcomes with fatality rate of 5.88 % and abortion rate of 17.64% [6,11]. In recent decade, to our knowledge, such severe clinical complications have not been reported in China. However, elevation of the liver injury marker ALT has been reported in pregnant women with anti-HEV IgM positivity in Yunnan [15], but not in Jiangsu province [14]. Genotype 4 HEV infection-associated adverse feto-maternal outcomes among pregnant women were reported in Qinhuangdao, but no death occurred [10]. In our study, we observed a slight elevation of ALT, and potential relation to pregnant hyperlipidemia in the participants with recent/ongoing HEV infection. However, the patient number of anti-HEV IgM positive was too small to draw firm conclusions.

Vertical transmission from HEV infected mothers can cause poor fetal and neonatal outcomes [32,33]. The risk of vertical transmission was 100% in an antecedent study among the pregnant women. The mothers with active diseases gave birth to babies who were either preterm or had anicteric hepatitis [34]. Similarly, in another study, among the 186 deliveries, 84% were preterm. But a significantly increased risk of preterm deliveries occurred in HEV-infected women [28]. In our study, the babies born to mothers with anti-HEV IgM antibody positive were inclined to preterm (14.3%) or jaundice (23.5%) compared to those only with anti-HEV IgG antibody positive. Again, because of limited number of anti-HEV IgM positive patents, the effects on fetal and neonatal outcomes require to be further validated.

There are some limitations in this study. We did not collect information regarding the history of women with HEV prior to enrollment or in the follow-up. These data may be helpful for better understanding the risk factors for HEV infection. Pregnant women may be co-infected with other hepatotropic pathogens, which may also contribute to the clinical outcomes, but these were not tested in this study. We could not detect HEV RNA, therefore fail to confirm the exact genotype. Finally, the patient number with anti-HEV IgM positivity was too small to draw firm conclusions.

In summary, we report the rate of HEV sero-prevalence of 6.62% among pregnant women in Inner Mongolia, China, with IgG antibody positivity of 6% and IgM antibody positivity of 0.6%. Importantly, recent/ongoing HEV infection might be associated with a slight increase in adverse pregnancy outcomes, obstetric complications, and poor fetal/neonatal outcomes. However, the patient number recent/ongoing HEV infection was too small and caution should be taken in interpreting the clinical outcome associations. Thus, future research is warranted to further confirm our findings in large populations in China, in order to better understand and control this health issue.

Author contributions

All authors (XM, YJ, LJ, DZ, YW, ZM and QP) were involved in the concept and design of the study; XM, YJ, LJ, ZB and DZ collected the data and conducted the analyses, the results were interpreted by all authors. XM drafted the manuscript which was critically revised by QP, YW and ZM, and approved by all authors. ZM and XM obtained the funding for the project. QP and ZM supervised the project.

Conflict of interest

The authors do not have any disclosures to report.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.clinre.2020.08.012.

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