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Retrospective Cohort Study

Pregnancy and fetal outcomes of chronic hepatitis C mothers with viremia in China

Pregnant Outcomes and Transmission of Hepatitis C

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Abstract

BACKGROUND

Data that assess the maternal and infant outcomes in Hepatitis C virus (HCV)-infected mothers is limited.

AIM

We aimed to investigate the frequency of complications and the associated risk factors.

METHODS

We performed a cohort study to compare pregnancy and fetal outcomes of HCV-viremic mothers with those of healthy mothers. Risk factors were analyzed with Logistic regression.

RESULTS

Among 112 consecutive HCV-antibody positive mothers screened, we enrolled 79 viremic mothers. We randomly selected 115 healthy mothers from the birth registry as the control. Compared to healthy mothers, HCV mothers had a significantly higher frequency of anemia (2.6% [3/115] vs. 19.0% [15/79], $p<0.001$) during pregnancy, medical conditions that required caesarian section (27.8% [32/115], vs. 48.1% [38/79] p=0.003), and nuchal cords (9.6% [11/115] vs. 34.2% [27/79], p<0.001). In addition, the mean neonatal weight in the HCV group was significantly lower (3,278.3±462.0 *vs* 3,105.1±459.4 gms; P = 0.006) and their mean head circumference was smaller (33.3±06 *vs* 33.1±0.7 cm; P = 0.03). In a multivariate model, HCV-infected mothers were more likely to suffer anemia (adjusted OR 17.5, 95%CI 4.2-72.8), require caesarian sections (adjusted OR 2.7, 95%CI 1.4-5.0), and have nuchal cords (adjusted OR 5.8, 95%CI 2.5-13.4). Their neonates were also more likely to have smaller head circumferences (adjusted OR 2.1, 95%CI 1.1-4.3) and lower birth weights than the average (≤3250 gms) with an adjusted OR of 2.2 (95%CI 1.2-4.0). The vertical transmission rate was 1% in HCV-infected mothers.

CONCLUSION

Maternal HCV infections may associate with pregnancy and obstetric complications. We demonstrated a previously unreported association between maternal HCV viremia and a smaller neonate head circumference, suggesting fetal growth restriction.

Key Words: HCV viremia; Mother to child transmission; Pregnancy complications; Maternal health; Infant HCV infection

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Core Tip: Although HCV affects a significant number of pregnant women, there is limited data regarding the impact of HCV active infection on pregnancy and infant outcomes. The current cohort study compared maternal complications and fetal development of HCV mothers with detectable levels of HCV RNA with those of healthy mothers. The study demonstrates a previously unreported association between maternal HCV viremia and a smaller neonate head circumference. In addition, HCV viremia was an independent predictor for negative maternal outcomes including anemia during pregnancy, medical conditions that required caesarian section, and nuchal cords. These findings increase the need for close antenatal surveillance in HCV mothers with viremia for maternal complications and delayed fetal development.

INTRODUCTION

Hepatitis C virus (HCV) infection is a common infectious disease in the liver and remains a significant global health burden [1]. Although spontaneous viral clearance may occur in approximately 15% of patients who have acute HCV infection, the majority develop a chronic liver infection with HCV. Among patients who have chronic

hepatitis C, about 10-15% will progress to cirrhosis within the first 20 years of infection, which eventually become decompensated without appropriate therapy or gain a high risk of developing liver cancer [2]. The prevalence of antibodies to HCV (HCV-Ab) in pregnant women is 0.1% to 2.4%, although it is much higher in some endemic areas [3]. The proportion of pregnant women with HCV-Ab positive whose active infection with viremia is about 60% to 70% [3].

Globally, up to 8% of pregnant women are infected with HCV in high endemic areas [4]. In the US, surveillance published in 2017 reveals a nationwide increase in HCV infection among pregnant women, which is an increasing but potentially modifiable threat to maternal and child health [5]. The proportion of infants born to HCV-infected women is also increasing in the US [6]. It has been reported that vertical transmission is the most common mechanism of HCV infection for children, which occurs in approximately 6% of infants born to women with HCV infection [7]. The risk of HCV vertical transmission increases if the maternal serum HCV viral load is above 10^5 copies/mL[8, 9]. In addition, published studies suggested that vertical transmission encompasses several potential transmission routes from an infected woman to her newborn, which include intrauterine, intrapartum, and postnatal [10-13]. According to the American Association for the Study of Liver Diseases (AASLD) guidelines, all pregnant women should be tested for HCV infections, ideally at the time of initiation of prenatal care [14].

Although HCV affects a significant number of pregnant women, there is limited data regarding the impact of HCV active infection on pregnancy and infant outcomes. Prior studies of HCV and pregnancy have focused on the vertical transmission rates of HCV infection using the limited assessments of the effects of chronic HCV infections on maternal health, complications during delivery, and fetal complications [15]. Therefore, there are data gaps in supporting strategies for clinical management of mothers with HCV infections during pregnancy. Also, the identification of adverse consequences could improve current perinatal care and monitoring recommendations. With that in mind, we conducted a retrospective cohort study to compare the frequency and severity

of adverse maternal outcomes during pregnancy, as well as fetal and infant outcomes between mothers with HCV viremia and healthy mothers.

MATERIALS AND METHODS

Study design, setting, and patient selections

This is a single-center retrospective observational cohort study conducted at a tertiary referral university hospital located in Shijiazhuang city of Hebei province in China, which receives referrals from different levels of community medical clinics and health facilities in the city. The study site is catering mainly to mothers with infectious diseases including hepatitis B, hepatitis C, and human immunodeficiency virus (HIV). The Institutional Review Board approved the study, and the need for informed consent was waived. Local standards of care for prenatal care include regular clinic visits about every 4 to 6 wk during pregnancy for mothers who are infected with chronic viral hepatitis. Mothers received a symptom-directed physical exam, blood tests, and ultrasonography exams from the early second trimester to delivery. Viral hepatitis and HIV screening were performed at the first prenatal visit (often during the first or early second trimester), and hospital delivery was mandated in the entire province except in an emergency event.

In the current study, patients who attended the services in the prenatal care clinic from November 1st, 2011 to May 31st, 2020, were screened for eligibility. Adult patients (age >18 years old) who had a diagnosis of HCV-Ab positive at least six months and also detectable levels of HCV RNA (>15 IU/mL) during prenatal screening were eligible for enrollment. Major exclusion criteria were the following: co-infection with hepatitis B virus, hepatitis D virus, or human immunodeficiency virus; current or history of intravenous drug use or sexually transmitted diseases; liver cancer; autoimmune liver disease; primary biliary cirrhosis; and alcohol-related liver diseases (consumption of more than 20 g/day of alcohol for > 5 years). Patients with other liver diseases, including inherited liver diseases and drug-induced liver injury, were also excluded. For each patient included in the HCV group, a healthy mother was identified

and selected from the Delivery Suite Registry at random. The selection was based on their infants' date of birth (±30 days) matched to those of HCV mothers with similar baseline values (matched for gestational days and parity). Based on the ratio of approximately 1:1 to match the number of subjects enrolled in the HCV group, a similar number of subjects was included in the healthy mother group. All patients included in the study were not smoking, drinking alcohol, or using any recreational drugs since these variables may affect the infants' outcomes.

Laboratory measurements for subjects in the study were all performed by the central laboratory in the medical center. HCV-Ab was tested by the chemiluminescent microparticle immunoassay (Autobio, Zhangzhou, China). Serum HCV RNA levels were measured with the real-time quantitative PCR method by using the Cobas TaqMan polymerase chain reaction assay according to laboratory manuals (Roche Diagnostics, USA). The undetectable level was defined as below the lowest level of quantitation = 15 IU/mL. The comprehensive chemistry panel was tested using a HITACHI 7600 fully-automatic biochemical analyzer, with the ULN of ALT set at 40 U/L (Wako Pure Chemical Industries, Ltd. Japan).

Patient data collection and outcome assessment

Using an electronic medical record system and paper charts, we collected the following maternal data: patients' demographic information and pertinent clinical data including a history of liver disease or hepatocellular carcinoma, pregnancy and obstetric complications, medication lists, positive physical findings including pelvimetry, labor outcomes, modes of delivery, laboratory results of completed blood count, coagulation tests, chemistry panels with alanine aminotransferase (ALT), virological tests, and imaging results if available. Pertinent data were assessed in all the visits starting from gestational week 12 with a four-week interval before delivery, at delivery, and postpartum weeks 12, 24, and 36. Perinatal information for fetal development, including birth weight, height, Apgar scores, gestational age, and perinatal complications like birth trauma and neonatal jaundice, was extracted from the

neonatal records. Infant outcomes like intrauterine growth restriction, birth defects, macrosomia, low birth weight, and meconium staining stool were collected.

The primary assessment was to analyze the frequency of maternal complications (both pregnancy and obstetrics complications) and negative fetal outcomes in HCV-infected mothers with viremia *vs* those in healthy mothers. In addition, vertical transmission rates were analyzed among mothers with HCV infection. Secondary assessments were the association between demographic or clinical features and the negative maternal or fetal outcomes in a multivariable logistic regression analysis. The current study used the following criteria to define the vertical transmission of HCV and considered the transmission confirmed if any of the following occurs: (1) detection of HCV RNA in an infant who is 3 to 6 mo old; (2) detection of HCV RNA in the infant on at least 2 occasions; (3) finding elevated serum aminotransferase levels in the HCV-Ab positive child (ULN=40 U/mL); or (4) confirming identical genotype between mother and child [3].

Statistical analysis

Data analyses were performed using the Statistical Package for Social Science for Windows, Version 25.0 (SPSS Inc., IBM, New York, USA). Frequencies and percentages were used to summarize categorical variables. Fisher exact tests or Chi-squared tests were used when comparing data between and within groups. Depending on the underlying distribution of the data, descriptive values were expressed as means ± standard deviations or medians and interquartile ranges (IQR). The student's t-test was used to assess continuous variables between groups. The maternal outcomes or infant outcomes were calculated per pregnant mother and/or per infant when appropriate. The baseline demographic or characteristic variables were analyzed as independent variables, whereas the negative maternal or infant outcomes were considered as dependent variables. Risk factors identified from the univariate analysis (p-value < 0.05) were further analyzed in the multivariate logistic regression model. The aforementioned risk factors associated with negative outcomes were presented with crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs). All tests were

two-tailed with a 95% confidence interval and the p-value < 0.05 was considered significant.

RESULTS

Patient characteristics

Among the 122 consecutive HCV antibody-positive pregnant women screened, 30 were not eligible due to undetectable levels of HCV RNA throughout the pregnancy. In addition, 13 patients were excluded because they were co-infected with HIV (n = 6) or hepatitis B virus (n = 7). As a result, seventy-nine patients who had HCV viremia during pregnancy were eligible for the HCV group. In addition, 115 healthy mothers were identified and selected from the Delivery Suite Registry at random (delivery date ±30 days matched to those cases in the HCV-infected group with similar baseline variables). As a result, our cohort consisted of 194 pregnant women with 79 and 115 mothers in the HCV group and a healthy mother (non-infected) group, respectively. The patient selection process is shown in Figure 1. All patients in the HCV group had no clinical indicator for liver decompensation. The clinical characteristics of the study patients are presented in Table 1. The demography characteristics were well matched between the two groups in the majority of variables, including pre-pregnancy mean BMI, numbers of parity or plurality, mean gestational days, and mean ALT at delivery. However, mothers in the healthy group had a significantly older mean age (29.4±4.9 *vs* 25.8+4.7 years, p<0.001), low frequency of intertuberous diameter <8.5 cm (29.6% *vs* 48.1%, P = 0.009), and were taller (160.9+4.0 *vs* 159.6+3.8 cm, p<0.001) when compared to those in the HCV group.

Maternal outcomes

Data from the gestational week 12 to delivery on pregnancy or obstetric complications and maternal laboratory abnormalities were analyzed. The following pregnancy and obstetric negative outcomes were identified either in the HCV infected mothers or healthy mothers (Table 2): preterm labor, preeclampsia, eclampsia, gestational hypertension, anemia, abnormal renal or thyroid function, oligohydramnios,

gestational diabetes, nuchal cord, umbilical cord prolapses, postpartum hemorrhage, premature rupture of membranes, and cesarean section due to medical needs. When comparing the aforementioned outcomes or laboratory abnormalities between the HCV-infected and healthy individuals, a significantly higher frequency of anemia during pregnancy was observed in the HCV group (19.0% [15/79] *vs* 2.6% [3/115], p<0.001). In addition, a significantly higher frequency of nuchal cords (34.2% [27/79] *vs* 9.6% [11/115]; p<0.001) and cesarean sections due to medical needs (48.1% [38/79] *vs* 27.8% [32/115]; *P* = 0.004) was reported in the HCV group. The frequency of other pregnant or obstetric complications did not differ between the two groups (Table 2).

Fetal and infant outcomes

When comparing the fetal and infant outcomes between the HCV-infected and the healthy mothers' groups (Table 3), we observed a significantly lower mean (SD) body weight in neonates who were born to HCV-infected mothers (3,105.1±459.4 *vs* 3,278.3±462.0 gms; *P* = 0.006). However, the frequency of low birth weight (<2500 gms) did not differ between the two groups (8.9% [7/79] *vs* 3.5% [4/115]; *P* = 0.20). The other variables did not differ between the two groups. In addition, neonates in the HCV group had a significantly smaller mean head circumference (33.1±0.7 *vs* 33.3±06cm; *P* = 0.03). The other measurements did not differ between the two groups, which included gestational weeks, the percentage of neonates that reached full-term or small for gestational age at delivery, and the mean height at birth. There were no miscarriages, stillbirths, birth defects, or Apgar scores <7 at 5 minutes after the birth were reported in the entire cohort.

Among infants who were born to HCV-infected mothers, all were tested HCV-Ab positive at birth and one had a detectable level of HCV RNA (2165 IU/mL). All infants in the study cohort were breastfed. Their HCV-Ab became negative beyond six months, except for the one who had HCV viremia at birth. This infant continued to have HCV antibodies and detectable levels of HCV RNA measured at the ages of three months and nine months, meeting the criteria of chronic hepatitis C infection. The HCV transmission rate in our study was 1.3% (*n* = 1/79). In the review of maternal

characteristics, the mother was 25 years old with a maternal HCV RNA level of 2.58 × 5 Log_{10} IU/mL at delivery. She had a history of blood transfusion and was diagnosed with chronic HCV infection during prenatal screening. Her pregnancy was uneventful with normal levels of ALT throughout the entire pregnancy. She delivered a girl with normal physical developments at the gestational week 39 plus 5 days.

Risk factors associated with negative outcomes

When comparing the pregnancy and obstetric complications between the two groups, we identified that a significantly higher frequency of anemia, nuchal cord, and cesarean section due to medical needs occurred among HCV-infected mothers. The crude and adjusted ORs with 95%CIs of each risk factor are presented in Table 4. The analyses indicated that HCV infection was the only factor associated with anemia (adjusted OR 17.5, 95%CI 4.2-72.8), increased numbers of C sections due to medical needs (adjusted OR 2.7, 95%CI 1.4-5.0), and Nuchal cords during pregnancies (adjusted OR 5.8, 95%CI 2.5-13.4). Since a significantly smaller head circumference and lower mean birth weight were the only two negative fetal outcomes identified in infants from HCV-infected mothers, we analyzed the maternal risk factors (Table 5) and found that maternal HCV infection was associated with these negative outcomes. The adjusted ORs of maternal HCV infection associated with smaller head circumference and birth weight ≤3250 gms were 2.1 (95%CI 1.1-4.3) and 2.2 (95%CI 1.2-4.0), respectively.

DISCUSSION

Although HCV vertical transmission can occur in up to 5.8% of mother-infant pairs,[16] many children can clear HCV infection spontaneously.[17] The disease can also be cured with oral antiviral therapy starting at the age of 3.[17] Therefore, the clinical landscape on managing HCV-infected mothers has recently shifted from addressing HCV vertical transmission to the assessment and management of negative pregnancy or neonatal outcomes. Published studies have linked several negative pregnancy outcomes to maternal HCV infection, including intrahepatic cholestasis, [18-20] gestational

diabetes,[21-23] the premature rupture of the membrane, [24, 25] the requirement of cesarean delivery, [24, 25] preterm delivery,[23] small for gestational age, [26] and low birth weight.[26] However, the restriction or disturbance of intrauterine fetal growth remained inconclusive. [21, 23, 26-28]

Our study assessed both maternal and fetal outcomes in viremic mothers with HCV infections. To our knowledge, this is the first study from China to assess the pregnancy outcomes in HCV viremic mothers. We identified that HCV may associate with a higher frequency of nuchal cords and a smaller neonatal head circumference, which has not been reported in the literature before. We also found that HCV viremia was linked to pregnancy anemia, cesarean sections due to medical needs, and low gestational weight in neonates. In addition, we observed that lower birth weight was associated with maternal infection, which was consistent with published data from the US and Europe.[23, 26] In the context of all infants in our study being breastfed, the HCV vertical transmission rate was 1.27%, which was within the range (0.2 - 6%) of the already published studies. [16, 29]

Early studies by Jeffery *et al* and Bohman *et al* found that fetal outcomes did not differ between HCV-positive mothers and the health control. [30, 31] However, in a study by Salemi *et al*, the risk of an adverse neurological outcome was higher in infants born to HCV mothers, including feeding difficulties (OR: 1.32, 95%CI = 1.06-1.64) and neonatal seizures (OR = 1.74, 95%CI = 0.98-3.10). [27] The aforementioned studies have limitations of lacking a well-defined study population because the diagnosis of HCV was based on the HCV-antibody, and the HCV RNA was not always tested. Paternoster *et al* observed that intrahepatic cholestasis was more common in HCV-RNA positive mothers than in HCV-RNA negative mothers, suggesting that HCV viremia may lead to different outcomes. [19] In addition, cofounders such as intravenous drug use or sexually transmitted diseases may not be adjusted in studies based on pregnancy registries. [26, 32] These factors could contribute to the discrepancy among the study findings. In the context of the paucity of data and infrequency of a fetal negative event, Huang *et al*

performed a meta-analysis and found that low birth weight was linked to maternal HCV infection (OR 1.97, 95% CI 1.43-2.71).[32]

In our study, the birth weight ≤3250 gms was associated with HCV exposure. There was also a trend in the HCV-exposed neonates with a birth weight of <2500 gms. More importantly, our cohort demonstrates a previously unreported association between maternal HCV viremia and a smaller neonate head circumference. Our findings provide new evidence supporting the intrauterine restriction of fetal growth in a well-defined HCV population, which enrolled only HCV-infected mothers with detectable levels of HCV RNA who had no history of intravenous drug use or sexually transmitted diseases.

Although the mechanism of fetal growth restriction is not fully understood, several studies suggested that HCV-induced inflammation in the placenta may cause fetal development restriction. In vitro study, HCV infects a human cytotrophoblast and changes its ultrastructure dramatically upon infection. [33] In addition, Hurtado *et al* observed that the cytotoxicity of natural killer cells and natural killer T cells was enhanced in the placenta, and placental natural killer T cell cytotoxicity was further increased by HCV infections. [34] Several population-based retrospective cohort studies reported higher rates of gestational diabetes in HCV-infected mothers compared with noninfected mothers,[35-37] and the association was limited to women with excessive weight gain during pregnancy. Our study did not show such complications, which is likely because our patients are Ascians with much lower body mass index when compared to other studies.[21, 24, 26]

In this cohort study, some limitations should be addressed. Being a single-center retrospective design, this study has a limited capacity when adjusting or balancing all covariates between the HCV-exposed and HCV non-exposed groups. Additionally, we did not have HCV genotype data. However, published studies in China indicated that the majority of Chinese patients with HCV had genotype 1.[38] Secondly, cohort data about HCV-antibody positive but nonviremic mothers is limited: these mothers were not enrolled in our study due to the small number of patients in our center (n = 30,

figure 1). Further studies in this sub-group will add to the understanding of their pregnancy outcomes. Thirdly, the liver fibrosis stages for patients with HCV infection were not assessed in the study although all patients had no clinical indicator for liver decompensation. Therefore, future studies might be needed to investigate if HCV-infected patients with advanced fibrosis have negative maternal and fetal outcomes. Lastly, the frequency of negative events in HCV-infected mothers could be underestimated due to the maternal mean age being younger than that of healthy mothers.

CONCLUSION

In conclusion, our study demonstrates a previously unreported association between maternal HCV viremia and a smaller neonate head circumference. Given our new findings on the intrauterine restriction of fetal growth from HCV exposure, screening of all mothers during pregnancy for HCV should be a mandatory practice. More importantly, our findings increase the need for close antenatal surveillance in HCV mothers with viremia for maternal complications and delayed fetal development. Lastly, our data support that preconception health management should include HCV screening, so HCV infection can be treated before pregnancy to improve the health of both the mothers and infants.

ARTICLE HIGHLIGHTS

Research background

Hepatitis C virus (HCV) infection remains a significant global health burden, and there is a high proportion of women with HCV-Ab positive whose active infection with viremia. In addition, HCV infection among pregnant women is an increasing but potentially modifiable threat to maternal and child health.

Research motivation

Although HCV affects a significant number of pregnant women, there is limited data regarding the impact of HCV active infection on pregnancy and infant outcomes. Therefore, there are data gaps in supporting strategies for clinical management of mothers with HCV infections during pregnancy.

Research objectives

we conducted a retrospective cohort study to compare the frequency and severity of adverse maternal outcomes during pregnancy, as well as fetal and infant outcomes between mothers with HCV viremia and healthy mothers.

Research methods

A retrospective observational cohort study was conducted to compare pregnancy and fetal outcomes of HCV-viremic mothers with those of healthy mothers. After HCV mothers with viremia and healthy mothers were enrolled, we collected their demographic information and pertinent clinical data using an electronic medical record system and paper charts. Perinatal information for fetal development and infant outcomes were extracted from the neonatal records. Data analyses were performed using the Statistical Package for Social Science for Windows, Version 25.0 (SPSS Inc., IBM, New York, USA).

Research results

Our study enrolled 79 viremic mothers and 115 healthy mothers. Compared to healthy mothers, HCV mothers had a significantly higher frequency of anemia, caesarian section, and nuchal cords during pregnancy. In addition, the mean neonatal weight and head circumference in the HCV group was significantly lower. In a multivariate model, similar results were found.

Research conclusions

Our study demonstrates the association between maternal HCV viremia and a smaller neonate head circumference, and confirmed the high frequency of pregnancy and obstetric complications in HCV viremic mothers.

Research perspectives

Multi-center and large sample studies are needed to verify these results in the future, and to investigate if HCV-infected patients with advanced fibrosis have negative maternal and fetal outcomes.

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