JOURNAL OF VIRAL HEPATITIS
JVH

Journal of Viral Hepatitis, 2015, **22,** 1033–1042 doi:10.1111/jvh.12430

Chronic hepatitis C virus infection is associated with increased risk of preterm birth: a meta-analysis of observational studies

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Received December 2014; accepted for publication February 2015

SUMMARY. Although several epidemiological studies reported that maternal chronic hepatitis C virus (HCV) infection had significantly increased risk of undergoing adverse obstetrical and perinatal outcomes, studies on the relationship between HCV infection and risk of preterm birth (PTB) have yielded inconclusive and inconsistent results. Therefore, we conducted a meta-analysis to investigate the association between HCV infection and PTB. The electronic database was searched until 1 September 2014. Relevant studies reporting the association between HCV infection and the risk of PTB were included for further evaluation. Statistical analysis was performed using REVMEN 5.3 and STATA 10.0. Nine studies involving 4186698 participants and 5218 HCV infection cases were included. A significant association between HCV infection and PTB was observed (odds ratio = 1.62, 95% CI 1.48–1.76, $P < 0.001$, fixed-effects model). Stratification according to maternal smoking/alcohol abuse, maternal drug abuse or coinfected with HBV and/or HIV matched groups still demonstrated that women with HCV infection had a high risk for PTB. Findings from our meta-analysis suggested that maternal HCV infection was significantly associated with an increased risk of PTB. In the future, pathophysiological studies are warranted to ascertain the causality and explore the possible biological mechanisms involved.

Keywords: hepatitis C virus, pregnancy, preterm birth.

INTRODUCTION

Chronic hepatitis C virus (HCV) infection represents a major public health problem worldwide due to its burden of most chronic viral hepatitis cases in adults [1,2]. It is estimated that HCV infections are affecting more than 2.7 million people, with 33 000 new cases and 10 000 deaths per year [3]. The prevalence of HCV infection among women of reproductive age in the North America is approximately 1–4.8% [4–7]. The liver played a central role in regulating inflammation by its capacity to control both local and systemic inflammatory responses through different molecular mechanisms [8]. An increasing body of evidence recognizes the inflammatory response induced by HCV as a crucial link to the development of both liver injury (hepatitis, cirrhosis and hepatocellular carcinoma) and extrahepatic relative diseases (cardiovascular disease, metabolic disturbance and neurodegenerative disease) [9–13]. As the high prevalence of HCV infection has been observed in women during their reproductive age [5], one important issue was whether HCV infection could negatively impact on the pregnancy outcomes.

Preterm birth (delivery before 37 weeks' gestation) is the most common cause of neonatal morbidity and mortality and is also a leading global health issue [14,15]. The rates of preterm birth (PTB) have increased over recent decades. It was reported that the annual social economic burden associated with PTB in the United States had reached $26.2 billion as early as in 2005 [16]. Several epidemiological studies reported that maternal chronic HCV infection had significantly increased risk of undergoing adverse obstetrical and perinatal outcomes such as gestational diabetes mellitus [17–19], premature rupture of membranes [19], low birthweight infants and stillbirth [17–20]. However, the influence of HCV infection on preterm birth is not fully explored. During recent years, a number of studies assessed preterm birth in women with HCV infection [17–

Abbreviations: CIs, confidence intervals; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NOS, newcastle-ottawa quality assessment scale; PTB, preterm birth.

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25], but the results are inconsistent [20–25]. Thus, the possible role of HCV infection in the pathogenesis of preterm birth remains an important but unresolved issue.

To clarify these issues, we conducted a systematic review of the literature and a meta-analysis to investigate whether HCV infection was associated with an increased risk of PTB.

METHODS

The present meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [26].

Data sources and search strategy

Two independent investigators searched PubMed and Embase databases before 1 September 2014 using the combinations of terms 'virus' or 'viral' or 'HCV' or 'hepatitis C' and 'pregnancy outcome' or 'prenatal outcome' or 'perinatal outcome' or 'preterm' or 'labour' or 'delivery'. We sifted through potentially relevant articles, firstly by titles and abstracts, and then, we retrieved the full texts of articles for detailed review. Further, we scanned the reference lists of the articles that met the inclusion criteria in our analysis, and searched for those articles or citations in the Web of Knowledge, Google Scholar and Google to obtain additional studies.

Inclusion and exclusion criteria

Articles were included if they investigated the association between HCV infection before pregnancy and the risk of PTB among pregnant women *vs* non-HCV control groups. Studies included in this analysis defined chronic HCV infection status during pregnancy by the presence or absence of HCV antibody in blood during the first prenatal care visit or through medical records reviewed. PTB diagnosis was defined as delivery before 37 weeks' gestation. No language restrictions were used for study inclusion in this meta-analysis.

Data extraction

A form designed *a priori* was used to extract the information from the included studies. Two independent investigators performed the data extraction. PTB was the primary outcome measure. The following information was recorded: first author's last name, year of publication, study location, number of HCV participants with or without PTB, scoring of Newcastle-Ottawa Quality Assessment Scale (NOS) and covariates adjusted for in the analysis.

Assessment of methodological quality

Two independent investigators assessed the quality of each study included using the Newcastle-Ottawa Quality Assessment Scale (NOS) [27]. Studies of low, intermediate and high quality were defined with NOS scores of 1–3, 4–6 and 7–9 in the meta-analysis, respectively.

Statistical analysis

The pooled odds ratio (OR) with 95% confidence intervals (CIs) between HCV infection and PTB was used to estimate the effect sizes. The ORs were combined in a meta-analysis using a fixed-effects model when heterogeneity observed among studies was absent to moderate. When heterogeneity was high ($I^2 > 50\%$), a random-effects model was used. Heterogeneity among these studies was evaluated by two parameters. $P < 0.10$ for the Cochran's Q test or $I^2 > 50\%$ for Higgins statistic were regarded statistically significant heterogeneity [28]. The publication bias was investigated by two methods. Visual detection was used to analyze the funnel plots. Quantitative analysis of publication bias was performed by the Egger's regression asymmetry test [29]. Subgroup analysis was performed with respect to study type, maternal age, parity, smoking/alcohol abuse status, drug abuse status and coinfected viral diseases status in order to explore the influence of these factors on the association. Statistical analysis was performed using REVMEN 5.3 and STATA version 10.0.

RESULTS

Selection flow and study characteristics

The detailed search procedures are demonstrated in Fig. 1. Full texts of 12 identified articles were retrieved for further assessment. Three of these articles were excluded because they did not report the incidence of preterm birth. Finally, the remaining 9 independent articles were used for this meta-analysis. Of all the including studies, seven cohort studies and two case–control studies evaluated the ORs of preterm birth (Table 1). According to the NOS scoring (Table 2), all studies were of intermediate or high quality.

Main results

The pooled ORs from 7 cohort and 2 case–control studies are demonstrated in Fig. 2. Meta-analysis of these nine studies, involving 4186698 participants and 5218 HCV infection cases, suggested a significantly positive association between HCV infection and PTB (summary odds ratio = 1.62, 95% CI 1.48–1.76, $P < 0.001$, fixed-effects model) with mild heterogeneity among these studies ($Q = 7.05$, $I^2 = 0\%$, $P = 0.53$).

Subgroup analysis

An analysis of the results according to study type (cohort [17,19–23,25] or case–control [18,24]), maternal age

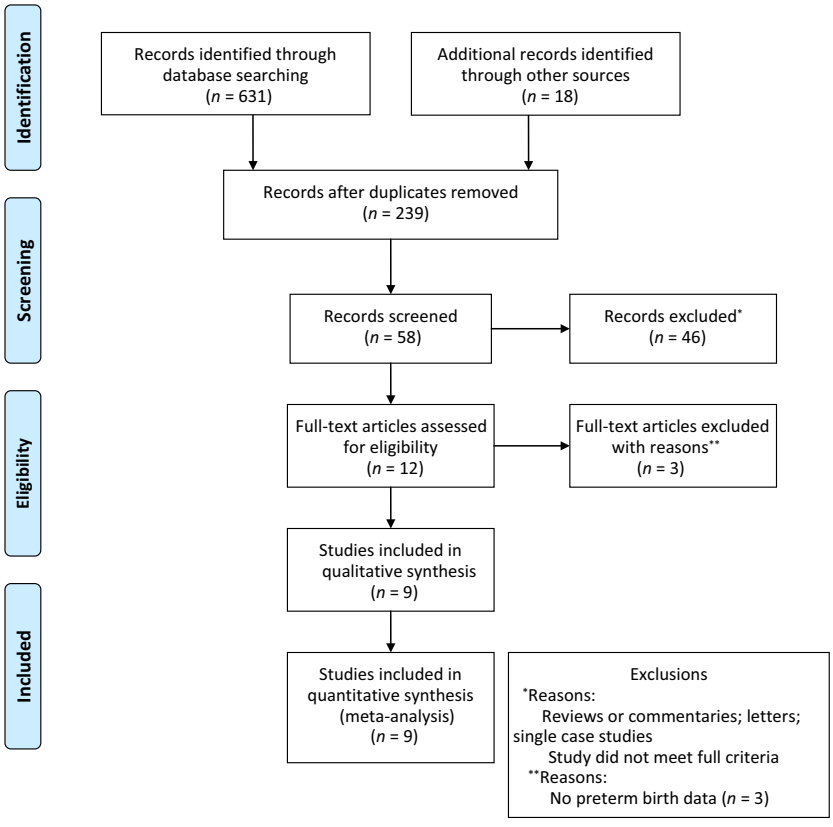

Fig. 1 Flow chart of the literature search and article selection.

(matched [18–19,21,23–25] or nonmatched/not reported [17,20,22]), maternal gravity and parity (matched [19–21,24,25] or nonmatched/not reported [17,18,22,23]), maternal smoking/alcohol abuse (matched [19,20] or nonmatched/not reported [17,18,21–25]), maternal drug abuse (matched [18–20] or nonmatched/not reported [17,21–25]), coinfected with hepatitis B virus (HBV) and/or human immunodeficiency virus (HIV) (matched [18,25] or nonmatched/not reported [17,19–24]) is summarized in Table 3.

Stratification according to maternal smoking/alcohol abuse, maternal drug abuse or coinfected with HBV and/or HIV matched groups still demonstrated that women with HCV infection have a high risk for PTB with no or mild heterogeneity observed.

Publication bias

Funnel plot with respect to the association between HCV infection and PTB did not demonstrate asymmetry which was typically associated with publication bias; Egger's regression asymmetry test suggested a low probability of publication bias ($P = 0.813$) (Fig. 3).

DISCUSSION

While previous studies demonstrated that maternal HCV infection was associated with increased risk of gestational diabetes mellitus, premature rupture of membranes, low birthweight infants and stillbirth [17–20], one intriguing observation was regarding the occurrence of PTB [20–25]. Previous reports on the association between HCV infection and risk of PTB have yielded inconsistent results. Our result demonstrated that maternal chronic HCV infection was significantly associated with increased risk of PTB.

Several mechanisms may be involved in the association between HCV infection and increased risk for PTB. Although the pathophysiology of PTB is not completely understood, local and/or systemic inflammations have been implicated as independent etiological factors of PTB [30,31]. Diseases characterized by chronic inflammation, such as Crohn's disease [32] and rheumatoid arthritis [33], were associated with an increased risk of PTB. Currently, a growing body of evidence indicated that chronic HCV infection was associated with both excessive hepatic and systemic inflammations [34,35]. Compared to HCV-negative individuals, increased levels of pro-inflammatory cytokines and a higher ratio of pro-inflammatory/anti-inflammatory cytokines have been reported in nondiabetic, nonobese HCV-infected patients [36,37]. Previous studies showed that a significant proportion of preterm births are associated with overproduction of pro-inflammatory cytokines [34]. Therefore, one possible biological interpretation for the higher incidence of PTB in women with HCV may be the results of excessive local and/or systemic inflammations triggered by the virus infection.

Table 1 Characteristics of studies of HCV *vs* control on preterm birth

Authors and year	Study type	Country	Characteristics of selected population	Fellow- up	Preterm/total	HCV diagnostic criterion or assay	HCV RNA(+)	Adjustment
Berkley *et al.* (2008) [20]	Retrospective cohort	USA	Pregnant drug-dependent women who referred to a state-supported drug abuse and treatment program at the University of New Mexico Hospital	2000–2006	HCV+: 39/159; HCV-: 21/141	NR	16/26	Parity, alcohol use, maternal drug use
Connell *et al.* (2011) [17]	Retrospective cohort	USA	All Florida births using birth certificate records linked to Healthcare Administration's Inpatient Hospital discharge data	1998–2007	HCV+: 129/988; HCV-: 147572/1669370	ICD-9	NR	NR
Hillemanns *et al.* (2000) [21]	Retrospective cohort	Germany	Pregnant women attending the antenatal clinic of the Department of Obstetrics and Gynecology, University of Munich.	1992–1996	HCV+: 9/31; HCV-: 699/3677	Anti- HCV (ELISA; WB) HCV- RNA (RT- PCR)	NR	Maternal age, parity
Jabeen *et al.* (2000) [25]	Retrospective cohort	Ireland	Review the birth history of 36 Rhesus-negative women that were infected HCV after their first pregnancy by contaminated anti-D immunoglobulin. The Control groups were age- and parity- matched Rhesus-positive women without any chronic illnesses.	1977–1978	HCV+: 4/89; HCV-: 2/63	Anti- HCV (ELISA; RIBA) HCV- RNA (RT- PCR)	26/36	Maternal age, parity, co-infected with HIV/HBV
Khaskheli *et al.* (2014) [23]	Prospective cohort	Pakistan	Women having obstetrical haemorrhagic emergencies at the Gynaecology and Obstetric University of Medical and Health Sciences Hospital	2009–2010	HCV+: 93/361; HCV-: 54/279	Anti- HCV (ELISA)	NR	Maternal age
	Case-control	India	Women who tested positive for anti-HCV antibodies at the	2003–2006	HCV+: 17/78; HCV-: 20/156	Anti- HCV (ELISA)	46/78	Maternal age, parity; prior

(continued)

Table 1 *(continued)*

Authors and year	Study type	Country	Characteristics of selected population	Fellow- up	Preterm/total	HCV diagnostic criterion or assay	HCV RNA(+)	Adjustment
Kumar *et al.* (2007) [24]			antenatal clinic of the first author and were delivered at the hospital during the study period.			HCV- RNA (RT- PCR)		history of liver Diseases.
Pergam *et al.* (2008) [19]	Retrospective cohort	USA	Review the Washington state singleton birth records linked to Comprehensive. Hospital Abstract Reporting System	2003–2005	HCV+: 82/500; HCV-: 127/2016	ICD-9	NR	Maternal age, parity, tobacco use, alcohol use, maternal drug use
Reddick *et al.* (2011) [18]	Case-control	USA	Review the National Inpatient data records on all pregnancy-related discharge.	1995–2005	HCV+: 92/555; HCV-: 35899/296218	ICD-9	NR	Maternal age, maternal drug use, co-infected with HIV
Salemi *et al.* (2014) [22]	Retrospective cohort	USA	Birth records linked to maternal and infant inpatient hospital discharge records in Florida	1998–2009	HCV+: 359/2457; HCV-: 198400/2214778	ICD-9	NR	NR

HCV, hepatitis C virus; HBV, hepatitis B virus; HIV, human immunodeficiency virus; NR, No reported; ICD, international classification of diseases; USA, United States of America; ELISA, enzyme linked immunosorbent assay; WB, western blot; RIBA, recombinant immunoblot assay; RT- PCR, reverse transcription- polymerase chain reaction; RNA, ribonucleic acid.

Table 2 Appraisal of methodological quality (Newcastle-Ottawa Scale) of the including studies

Study	Case-cohort representative	Selection of non-exposed control	Ascertainment of exposure	Outcome negative at start	Comparability by design	Comparability by analysis	Outcome assessment	Duration of follow-up	Score
Berkley *et al.* (2008) [20]	*	*	×	*	*	*	*	×	6
Connell *et al.* (2011) [17]	*	×	*	*	*	*	*	*	7
Hillemanns *et al.* (2000) [21]	*	*	*	*	*	*	*	*	8
Jabeen *et al.* (2000) [25]	*	*	*	*	*	*	*	*	8
Khaskheli *et al.* (2014) [23]	*	*	*	*	*	*	*	*	8
Kumar *et al.* (2007) [24]	*	*	*	*	*	*	*	*	8
Pergam *et al.* (2008) [19]	*	*	×	*	*	*	*	*	7
Reddick *et al.* (2011) [18]	*	*	×	*	*	*	*	*	7
Salemi *et al.* (2014) [22]	*	*	*	*	×	×	*	*	6

*Indicates that a feature is present; ×, that a feature is absent. But for comparability by design this checklist awards a maximum of two stars (**), one (*) or none if the feature is completely absence (×).

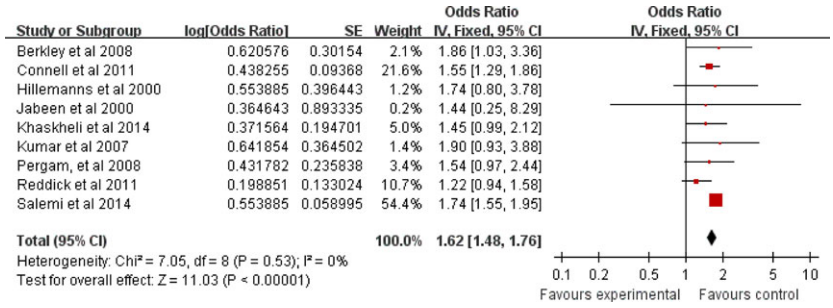

Fig. 2 Forest plot of the association between chronic hepatitis C virus infection and risk of preterm birth.

Table 3 Subgroup analysis of the association between HCV and preterm birth

	Studies	OR	95% CI	I^2 (%)
Study type				
Cohort	7	1.67	1.52–1.83	0
Case-control	2	1.29	1.01–1.64	23
Maternal age				
Matched	6	1.38	1.15–1.66	0
Not matched	3	1.69	1.53–1.86	0
Parity				
Matched	5	1.70	1.27–2.28	0
Not matched	4	1.61	1.47–1.76	54
Tobacco and/or alcohol use				
Matched	2	1.65	1.15–2.38	0
Not matched	7	1.61	1.48–1.76	12
Maternal drug use				
Matched	3	1.35	1.09–1.67	1
Not matched	6	1.67	1.52–1.84	0
Co-infected with HBV and/or HIV				
Matched	2	1.22	0.95–1.58	0
Not matched	7	1.67	1.53–1.83	0

HCV, hepatitis C virus; HBV, hepatitis B virus; HIV, human immunodeficiency virus.

A growing body of evidence linked placental dysfunction with increased incidence of pregnancy complications, especially low birthweight infants and PTB [38–40]. Prior studies suggested placental dysfunction in women with chronic HCV infection by providing consistent results of higher prevalence of low birthweight infants delivered by this specific population [17–20]. Moreover, although HCV is a hepadnavirus, mounting evidence suggested that it could also exist in extrahepatic tissues including kidneys [41], pancreas as well as ovaries [42,43], and even in placenta [44]. Trophoblasts are the main component cell types of placenta. A previous study showed that HCV could infect trophoblasts and alter the cellular ultrastructure [44], thus might lead to a compromised pregnancy. Therefore, another possible biological interpretation for the higher incidence of PTB may be the results of impaired trophoblasts and placental function caused by HCV infection.

Mounting evidence indicated that maternal cigarette smoking [45], alcohol abuse [46] and drugs abuse [47] before conception or during pregnancy were associated with higher incidence of PTB. Moreover, prior studies found that patients with HCV were associated with elevated rate of coinfected with HBV and/or HIV [48], which might negatively affect the obstetrical outcomes. It should be noted that several studies included in this meta-analysis

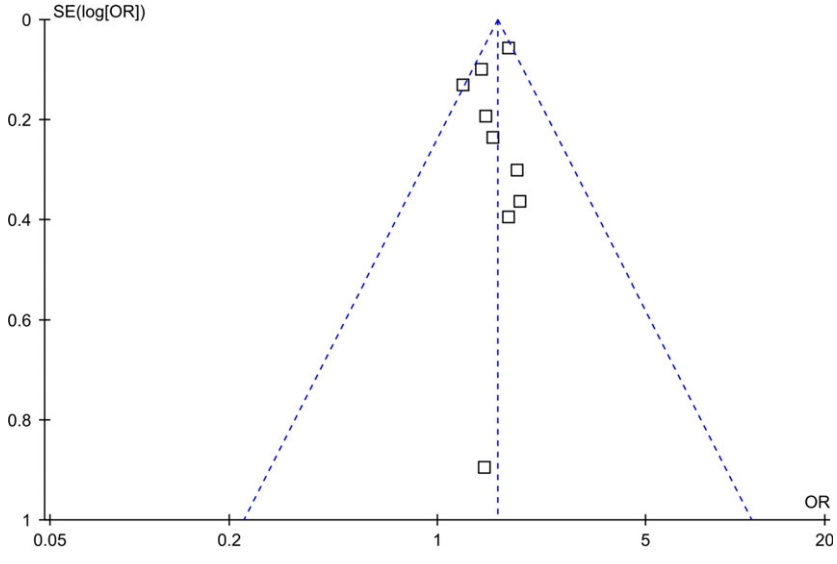

Fig. 3 Funnel plot of the association between chronic hepatitis C virus infection and risk of preterm birth.

also reported higher prevalence of maternal cigarette smoking, alcohol abuse, drugs abuse as well as coinfected with HBV and/or HIV in women with HCV infection [17–20,25]. Therefore, one might concern about whether these potential confounders could affect the overall pooled result. Our meta-analysis could avoid the influence of these crucial confounders, as we used adjusted ORs to estimate the effect sizes in this meta-analysis. Moreover, we performed a subgroup analysis according to maternal cigarette smoking, alcohol abuse, drugs abuse and coinfected status with HBV and/or HIV so as to further avoid the influence of these potential confounders. Although lower pooled ORs were observed when compared these crucial confounders between matched and unmatched groups, our results still demonstrated significantly positive association between HCV infection and PTB according to the matched groups, which indicated that maternal chronic HCV infection might be an independent risk factor for PTB.

Our meta-analysis has some strengths. First, a large number of participants and cases guaranteed the sufficient statistical power to get the reliable conclusions. Second, our findings provided a good estimation of the association between HCV infection and the risk of PTB, as no publication bias was observed and the heterogeneity was low among the studies included. Last but not least, our findings could avoid the influence of some potential confounders, as our results still demonstrated significantly positive association between HCV infection and PTB after subgroup analysis.

However, several limitations should be also addressed. First, the included studies were mainly performed in North America and Europe. Therefore, our findings might be not suitable to be applied to other populations. Second, two of the studies selected in this meta-analysis were case–control studies. Evidence from case–control studies could be probably of less accuracy and more influenced by recall bias when compared to those from cohort studies. In the future, prospective cohorts with larger samples sizes are warranted to ascertain the causality. Third, previous studies demonstrated that the copy number of HCV was highly associated with systemic inflammation and severity of diseases [49,50]. However, most studies included in this meta-analysis confirmed the HCV infection status through qualitative methods. Thus, we cannot perform a dose–response analysis to further investigate the association among HCV infection, systemic inflammation and the risk of PTB more precisely.

In conclusion, this meta-analysis evaluated the association between HCV infection and the risk of PTB and suggested that maternal HCV infection is significantly associated with an increased risk of PTB. In the future, pathophysiological studies are warranted to ascertain the causality and explore the possible biological mechanisms involved.

FUNDING

This work was supported by the President Grant from Nanfang Hospital (2012C026) to Dr. Qi Tao, Huang. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

COMPETING INTERESTS

The authors have no competing interests to declare.

ETHICAL APPROVAL

The study was approved by the local institutional review board.

AUTHOR CONTRIBUTIONS

QTH, MZ and YHY conceived and designed the experiments. QH, SSW and WL performed the experiments. QTH and FL analyzed the data. MZ and YHY contributed reagents/materials/analysis tools. QTH wrote the manuscript.

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